FORMULATION AND EVALUATION OF CONTROLLED RELEASE TABLETS OF PERINDOPRIL ERBUMINE

Dissertation Submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY,

Chennai-32

In partial fulfillment for the award of Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Reg. No. 26103013

Under the guidance of

Mrs. S. BHAMA, M.Pharm.,

Assistant Professor

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTRAJA COLLEGE OF PHARMACY

KOMARAPALAYAM – 638 183

TAMIL NADU

MAY -2012.

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF CONTROLLED RELEASE TABLETS OF PERINDOPRIL ERBUMINE",** submitted by the student bearing **[Reg. No. 26103013]** to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on…….

Internal Examiner **External Examiner**

CERTIFICATE

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PLACE: Komarapalayam
DATE:

Dr. P. PERUMAL, M.Pharm., Ph.D., A.I.C.,
Professor and Principal,
J.K.K. Nattraja College of Pharmacy,
Komarapalayam – 638 183, Tamil Nadu.

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Dr. R. Sambath Kumar, M. Pharm., Ph.D.,
Professor and Head,
Department of Pharmaceutics,
J.K.K. Nattraja College of Pharmacy,
Komarapalayam-638 183,
Tamil Nadu.

Mrs. S. Bhama, M. Pharm.,
Asst. Professor,
Department ofPharmaceutics,
J.K.K. Nattraja College of Pharmacy,
Komarpalayam-638 183,
Tamil Nadu.

DECLARATION

The work presented in this dissertation entitled "**FORMULATION AND EVALUATION OF CONTROLLED RELEASE TABLETS OF PERINDOPRIL ERBUMINE"** was carried out by me under the direct supervision of **Mrs. S. Bhama, M. Pharm.,** Asst. Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Komarapalayam, in partial fulfillment for the award of degree of Master of Pharmacy in Pharmaceutics.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other university.

PLACE: Komarapalayam **SURE NARESH KUMAR**

DATE : **Reg. No. 26103013**

ACKNOWLEDGEMENT

At the outset, I am thankful to my **PARENTS** and God for blessing me with great strength and courage to complete my dissertation. Behind every success there are lots of efforts, but efforts are fruitful due to helping hands making the passage smoother. So, I am thankful to all those hands and people who made my work grand success.

I take this opportunity with pride and immense pleasure expressing my deep sense of gratitude to our respectable and beloved guide **Mrs. S. BHAMA, M. Pharm.,** Asst professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Komarapalayam, whose active guidance, innovative ideas, constant inspiration, untiring efforts, encouragement and continuous supervision has made the presentation of dissertation a grand and glaring success.

I express my heartfelt thanks to respectable and beloved Principal **Dr. P. PERUMAL, M. Pharm., Ph. D., A.I.C.,** J.K.K. Nattraja College of Pharmacy, Komarapalayam, for furnishing all the necessary facilities with wholehearted support and guidance which enabled me for completing this dissertation in successful manner.

I am proud to dedicate my humblest regards and deep sense of gratitude and heartfelt thanks to late **Thiru. J.K.K. NATARAJAH CHETTIAR,** founder of our college providing us the historical institution to study. I wish to express my sincere thanks to our most respectful correspondent **Smt. N. SENDAMARAAI, B.Com,** Managing Director, **Mr. S. OMM SHARRAVANA, B.Com. LLB** and Executive director **Mr. S. OM SINGARRAVEL**, **B.E, M.S**., J.K.K. Nattraja Educational Institutions, Komarapalayam for their blessings, encouragement and support at all times.

My glorious acknowledgement to **Dr. K. SENGODAN, M.B.B.S.,** administrative officer for encouraging us in a kind and generous manner to complete this work.

My sincere thanks to **Dr. R. Sambath Kumar, M. Pharm., Ph.D.,** Professor and Head of the department**, Mr. K. Jaganathan, M. Pharm.,** Lecturer, **Mr. R. Kanagasabai, B. Pharm., M.Tech.,** Asst. Professor, Department of Pharmaceutics, for their valuable help during my project.

My sincere thanks to **Mr. V. Sekar, M. Pharm., Ph.D,** Professor& Head., **Mr. S. Jayaseelan, M. Pharm.,** Asst.Professor, **Mr. D. Boopathy, M. Pharm.,** Assistant Professor and **Mr. M. Senthilraja, M. Pharm**., **Ph.D,** Asst. Professor, Department of Pharmaceutical Analysis for their valuable suggestions.

I express my sincere thanks to **Mr. V. Rajesh, M. Pharm., Ph.D**, Professor & Head of the department, **Mrs. M. Sudha, M. Pharm.,** Lecturer, **Dr. P. Ashokkumar**, **M. Pharm., Ph.D,** Professor and **Mrs. R. Krishnaveni, M. Pharm,** Lecturer, Department of Pharmacology, for their valuable help during my project.

I express my sincere thanks to **Dr.P.Sivakumar, M.Pharm., Ph.D.,** Professor, **Mr.M.Vijayabaskaran, M.Pharm.,** Asst. Professor, **Mrs.P.Vaijayanthimala, M.Pharm.,** Lecturer, **Mrs.K.Mahalakshmi**, **M.Pharm.,** Lecturer, Department of Pharmacology, for their valuable suggestion and inspiration.

My sincere thanks to **Dr. S. Sureshkumar, M. Pharm., Ph.D.,** Professor& Head of the Department of Pharmacognosy and **Mr. M. K. Senthilkumar, M. Pharm.,** Asst.Professor, Department of Pharmacognosy for their valuable suggestions.

I express my sincere thanks to **Mr. N. Venkateswara Murthy,** M.Pharm., **Ph.D** Asst. Professor & Head, **Ms. S. Thangamani**, **M. Pharm.,** Lecturer, Department of Pharmacy practice for their valuable suggestions.

My sincere thanks to **Mr. N. Kadhiravel, M.C.A.,** for his help during the project. I am delighted to **Mrs. V. Gandhimathi, M.A., M.L.I.S.,** Librarian., **Mrs. S. Jayakla, B.A.,** Asst., for providing necessary facilities from Library at the time of Work. I extend my thanks to **Mr. S. Venkatesan**, Storekeeper, **Mr**. **Manikandan**, computer lab Assistant, and **Mrs. Shanthi,** our lab assistant for their help during the project.

I am thankful to all my classmates, friends, and juniors.

I pay **tribute** to **my lovable parents, Mr. S. Ramakoteaswara Rao my father**, **Mrs. S. Padmavathi my mother** for lifting me up till this phase of life. I sincerely thank them for their love, trust, patience and support and bearing all kinds of stress to make me what I am.

My truthful dedication to **My Brothers Mr. S. Suresh and S. Harish** whose blessings always with me.

It is very difficult task to acknowledge the services to thank all those gentle people. So I would like to thank all those people who have helped me directly or indirectly to complete this project work successfully.

SURE. NARESH KUMAR.,

(Reg.No. 26103013).

Dedicated to

almighty

My beloved parents,

Guide & my friends

CONTENTS

ABBREVIATIONS

S. No	Abbreviations	Description
1	#	Number
2	µm	Micrometer
3	%	Percentage
4	API	Active pharmaceutical ingredients
5	BCS	Biopharmaceutical Classification System
6	BP	British pharmacopoeia
7	f_1	Dissimilarity factor
8	f_2	Similarity factor
9	G	Gram
10	g/ ml	Gram per milliliter
11	GI	Gastrointestinal Tract
12	HPLC	High performance liquid chromatography
13	HPMC	Hydroxy propyl methyl cellulose
14	XG	Xanthan gum
15	ICH	International Conference on Harmonization
16	IP	Indian Pharmacopoeia
17	IPA	Isopropyl Alcohol

18	LOD	Loss on drying
19	MCC	Micro Crystalline Cellulose
20	mg	Milligram
21	mm	Millimeter
22	ml	Milliliter
23	N	Newton
24	NLT	Not Less Than
25	NMT	Not More Than
26	Ph Eur.	European Pharmacopoeia
27	µg	Microgram
28	PVP	Polyvinyl Pyrollidine
29	RH	Relative Humidity
30	rpm	Revolutions per minute
31	SR	Sustained release
32	CR	Controlled release
33	USP	United States Pharmacopoeia
34	UV	Ultra Violet
35	w/w	Weight per weight
36	w/v	Weight per volume

1. INTRODUCTION

The objective of any drug delivery system is to provide therapeutic amount of drug to targeted site in body to achieve the desired therapeutic effect. In recent years, attention has been focused on the development of new drug delivery system rather than invention of new molecules. Because the development cost for new drug molecule is very high and possibility of repenting successful drugs by applying concepts and techniques of controlled release drug delivery systems.

CONVENTIONAL DRUG DELIVERY SYSTEM

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms.

The oral dosage form has survived due to

1. Relatively simple and inexpensive to make

2. Convenient for the patient

3. Technology is easy to adapt to changing needs of the drug substance

4. Simplifies the regulatory approval process.

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid or immediate absorption[1].

Limitations of the Conventional Drug Delivery System

1) Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.
2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition is difficult.
3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range.

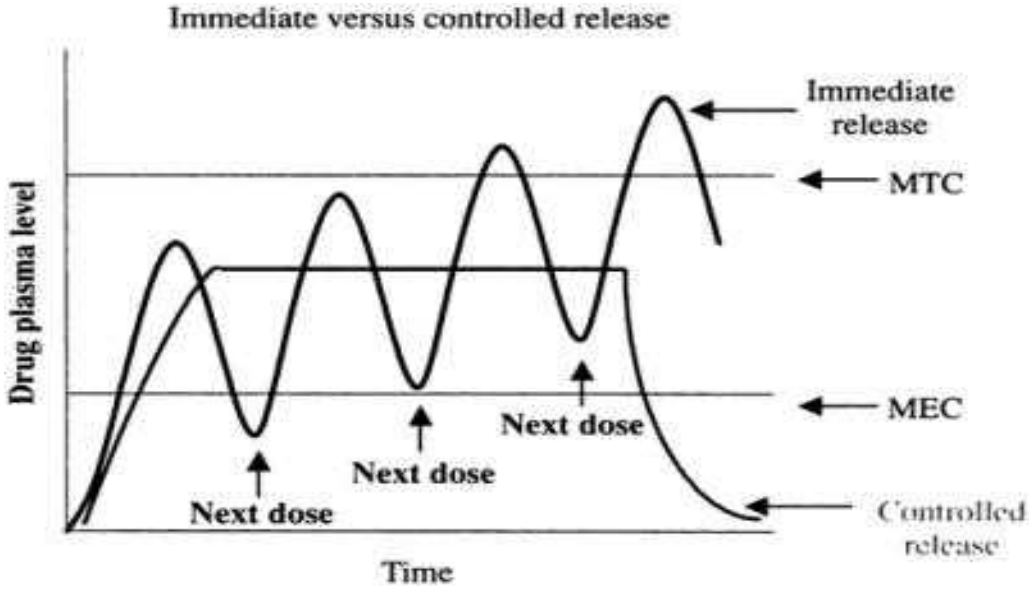
4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits[2].

For curing of disease, it is necessary to achieve and maintain the concentration of administered drug within the therapeutically effective range, for this drug dosage must be taken several times which results in fluctuating drug levels in plasma. This drawback of conventional dosage form can be overcome by formulation of controlled release dosage forms which provides drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with release profiles controlled by the special technological construction and design of the system.

The primary objectives of controlled drug delivery are to ensure safety and enhancement of efficacy of drug with improved patient compliance. So the use of these dosage forms are increasing in treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above minimum effective concentration and below the minimum toxic level for extended period of time. Thus, controlled drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects.

Figure No. 1 Immediate versus controlled release



Controlled Drug Delivery[1]

For many drugs, the basic goal of therapy is to achieve a steady state blood or tissue level i.e., therapeutically effective and non toxic, for an extended period of time. For this purpose controlled release dosage forms are designed.

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release depot and repository dosage forms are terms used for identifying drug delivery systems, which achieve prolonged therapeutic effect by continuous release of drug for extended time after single dose administration. controlled release systems release drug at predetermined rate and sustained release systems only prolong the drug release.

Advantages of controlled release dosage dorms

Controlled release preparations offer several advantages over immediate release conventional dosage form of same drug.

1. More efficient drug utilization by the body.
2. Better patient compliance.
3. Decrease in frequency of administration.

4. Elimination of peak and valley plasma levels so that drug concentration is maintained constant over a long period. Hence, reduction in severity and frequency of untoward effects.
5. Safety margin of potent drug is increased.

Disadvantages of controlled release dosage forms

1. Overdose: Being multiple preparations, there is always the possibility of sudden release of the total dose administered i.e. dose dumping, which may result in some toxic manifestations.
2. Loss and Flexibility in dosage: - It is very difficult to adjust the dose of controlled release products to a patient's response. The physician has less flexibility in adjusting the dosage regimen.
3. Side effects: - Controlled release preparations would show not only a longer duration of effect but also a long duration side effects, especially if patient is hypersensitive to given medication.
4. The cost of unit dose of controlled release system is higher than the regular conventional dosage forms.
5. Special treatment problems may arise during accidental poisoning with these systems.

Oral Controlled Drug Delivery System[4]

Oral route has been commonly adopted and most convenient route for the drug delivery, as the patient acceptance for oral route is high. It is relatively safe route of administration than most parenteral routes where the constraints of sterility and potential damage at site of administration are minimal. Controlled release preparation release the drug in controlled manner in gastrointestinal tract for systemic uptake.

As there is more flexibility and received more attention in designing of dosage form for oral route than drug delivery design for other routes.

Oral controlled delivery systems can be broadly classified into following categories, depending on their mechanism of drug release

1. Dissolution – controlled release
    a. Encapsulation dissolution control.
    b. Matrix Dissolution control.

2. Diffusion Controlled Release
    a. Reservoir devices
    b. Matrix devices

3. Water penetration Controlled
    a. Osmotically controlled release
    b. Swelling Systems.

4. Ion exchange resins
5. Gastro retentive Systems
6. Bio adhesive drug delivery systems.
7. Microspheres.
8. Spheronization/ Pelletization
9. Coating Technologies.

Dissolution Controlled Release System[5]

This can be obtained by slowing the dissolution rate of the drug. Slowing of dissolution rate can be achieved by incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness.

Also the drug may be incorporated in hydrophobic or hydrophilic matrix. The rate of penetration of dissolution fluid into matrix controls the rate of drug availability. Also the porosity of compressed structure is important parameter.

Matrix Formulations[6]

Matrix formulations are defined as a drug or other active ingredient embedded in insoluble excipients in order to achieve release by a continuous leaching of the drug from the inert matrix core.

Matrix systems can be divided into three types

1. Monolithic matrix tablets
2. Gel forming hydrophilic matrix tablets
3. Erodable (hydrophobic) matrix tablets

Inert monolithic matrix tablets

Probably the simplest method of obtaining controlled release of a drug from an oral dosage form is incorporation of a drug in an inert matrix. In this inert means non interacting with the biological fluids. The main reason for its popularity is that drug release from plastic matrix tablets is independent on the state and condition of the digestive juices, which may show large inter and intra patient variability (pH, viscosity).

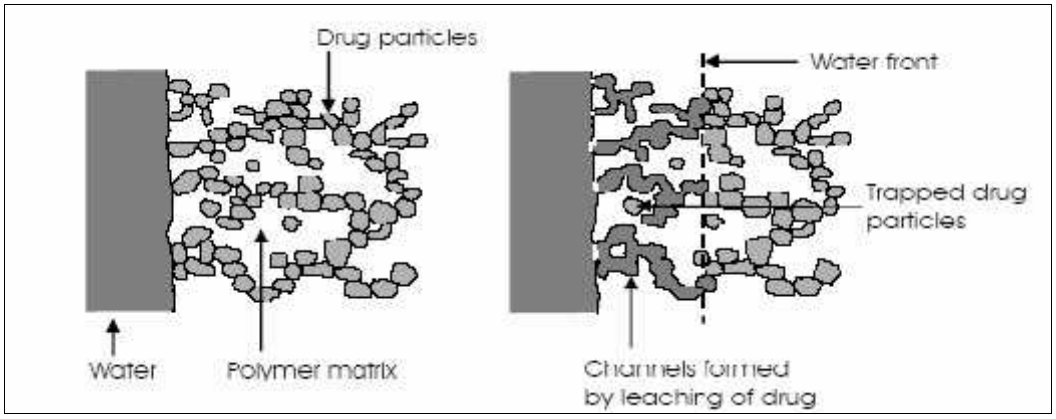
During its transit through the gastro-intestinal tract, the porous matrix tablet does not disintegrate like conventional tablets, but remains intact and the skeleton can be recovered in faeces. The materials used in the preparation of these inert matrices are predominantly (insoluble) polymers and lipophilic compounds. The first polymers to be used for the preparation of matrix tablets were (semi- synthetic polymers such as polyethylene, poly vinyl chloride, poly methyl methacrylate, polystyrene, poly vinyl acetate, cellulose acetate and ethyl cellulose. The fat compounds used included carnauba wax, hydrogenated castoroil, and tri stearin.

Major drawback of most of the inert polymeric matrix tablets were their inherent first order drug release characteristics, their poor direct compression characteristics and the problem leaning of agglomeration equipment used for the preparation of agglomerates with the required compression characteristics.

Mechanism of release of inert monolithic matrix tablets[10]

Release from inert matrix tablets occurs via a leaching mechanism. Drug particles dispersed in the polymer matrix dissolve in the penetrating gastro-intestinal fluids and are released from the tablet by diffusion through the porous network of already existing pores and pores that created by dissolution of the drug particles. At drug loadings exceeding approximately 10-15 % volume, a continuous structure connecting all drug particles exists (percolating drug network). At considerably lower loadings, a particular fraction of the drug may be completely surrounded by the polymer matrix (trapped fraction), which would result in incomplete release.

Figure: 2 Schematically representation of a leaching-based release mechanism.



Solvent activated matrix tablets

The use of solvent-activated matrix tablets as a method to obtain zero order release i.e. constant release rates over an extended period was first proposed by Hopfenberg. Solvent-activated drug delivery system is a collective term comprising

those systems in which the interact ion between polymer and water is responsible for achieving controlled release. The interaction with water may include plasticization, swelling, dissolution, erosion or degradation of the polymer. The two most important types of solvent activated matrix tablets are gel-forming hydrophilic matrix tablets and erodible (hydrophobic) matrix tablets.

Gel-forming hydrophilic matrix tablets

Gel-forming hydrophilic or swellable matrix systems are homogeneous or heterogeneous systems in which the drug is dispersed in a swellable hydrophilic polymer. These systems have been widely studied by researchers since they offer the possibility to obtain a constant drug delivery over an extended period of time. Drug release is a function of the polymer characteristics.

Upon swallowing gel-forming hydrophilic matrix tablets, the hydrophilic polymer is plasticized by the aqueous gastro-intestinal due to which undergoes macromolecular chain relaxation and volume expansion. Consequently, upon penetration of the gastro-intestinal fluids into tablet, a sharp front can be distinguished which separates a dry, glassy core from a hydrated and rubbery gel layer. Release is governed by diffusion of the dissolved drug through the swollen gel layer and generally shows a burst effect, caused by dissolution and leaching of drug particles present at the surface prior to formation of the release-controlling gel.

Other swellable polymers, which have been applied in swelling-controlled oral drug delivery systems, which show solvent controlled release, are guar gums, xanthan gum, poly (ethylene oxide) (PEO), poly (vinyl alcohol), ethylene-vinyl alcohol copolymers (EVA) and dextrans.

Erodible matrix tablets

Erodible polymers such as poly anhydrides offer another interesting material platform for zero-order drug release. Like several HPMC grades, upon water penetration, poly anhydrides form a gel-layer, which erodes at a specific rate. By choosing the right polymer composition the thickness of the gel-layer may remain constant with time resulting in a constant release rate until depletion of the drug.[12]

In the last two decades, controlled-release dosage forms have made significant progression terms of clinical efficacy and patient compliance. Preparation of drug- embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and since additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is commonly used for manufacturing controlled release dosage forms because it makes such manufacturing easy. A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. Polymers forming insoluble or skeleton matrices constitute the first category of retarding materials, also classed as plastic matrix systems.

The second class represents hydrophobic and water-insoluble materials, which are potentially erodible, while the third group includes polymers those form hydrophilic matrices.

Plastic matrix systems, due to their chemical inertness and drug embeding ability, have been widely used for controlling the release of the drug. Liquid penetration into the matrix is the rate-limiting step in such systems unless channeling agents are used. The hydrophobic and waxy materials, on the other hand, are potentially erodible and control the release of drug through pore diffusion and erosion. Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, does not disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier, which controls the drug release from, and the liquid penetration into the center of the matrix system.[13]

The use of hydrophilic polymers is actually the most used method in controlling the release of drugs in the formulation of oral pharmaceutical dosage forms. Hydroxy propyl methyl cellulose has been extensively used since the early1960s as a rate-controlling polymer in oral extended-release dosage forms.[14]

Hydrophilic matrix systems are popular and versatile controlled release system amongst polysaccharide derivatives like cellulose ethers, e.g. ,hydroxyl propyl methyl cellulose (HPMC) and a diverse range of other materials, including sodium alginate, carrageenan, chitosan, and xanthan gum.

Diffusion Controlled Release System

In case of diffusion controlled release system, diffusion of drug molecule through the polymeric membrane is the rate limiting step. These systems can be prepared by encapsulating the drug particles in polymeric membrane or by dispersing the drug in polymeric matrix.

These systems exhibit non-zero order release rate due to increase in diffusion resistance and decrease in effective diffusion area as the release proceeds.

Water Penetration Controlled Release System

In these systems, control release is obtained by the penetration of water into the system. There are following types of water penetration controlled release system,

Osmotically Controlled Release System

In this system delivery of drug is controlled by solvent influx across a semi permeable membrane which carries the drug outside through a laser drilled orifice.

The osmotic and hydrostatic pressure differences on either side of semi permeable membrane causes fluid transport into the system, so the rate of drug release is dependent on osmotic pressure of formulation.

Swelling Controlled Systems[11]

These systems are initially dry and when placed in body absorb water or other body fluids and swell. The drug is diffused through the swollen network. Thus, swelling and diffusion controls the release rate. Most materials used in swelling controlled systems swells without dissolving.

Ion Exchange Resins

The drugs which are susceptible for enzymatic degradation can be formulated using ion exchange resins as they temporarily protect the drugs. Resins are water insoluble materials having anionic, cationic groups. Complex of resin and drug is formed by prolonged exposure of drug to resin. In ionic environment drugs are displaced from the resin. The release rate is proportional to the concentration of ions present in the vicinity of administration site.

Gastro retentive systems

These are hydro dynamically balanced systems. In these systems dosage form have the specific gravity less than gastric juice, so they float in stomach and retain the drug over there for extended period of time. Thus, total residence time in stomach is increased. Also these systems are relatively large in size and passing from pyloric opening is prohibited.

This system is useful for drugs which are absorbed in stomach and also for local action of drug.

Bio adhesive Systems

Bio-adhesion is the attachment of synthetic or biological macromolecules to biological tissue. When bio-adhesion occurs with the mucus layer then it is called as mucoadhesion.

This type of dosage form results in

- Prolonged residence time within specified region of body and provides intimate contact with absorbing membrane.
- Localization of the drug delivery system at given target site.
- An increase in drug concentration gradient due to contact of drug particles with mucosal surface.
- Thus the combined effects of direct drug absorption and decrease in excretion rate causes increased bioavailability and duration of action with smaller dosage and less frequent administration.

Microspheres

These are monolithic, homogenous, spherical particles uniformly covered with polymer film. The size ranges from 0.1–100µm. They are widely used as drug carriers.

Administration of drugs in the form of microspheres causes

- Improvement of treatment as localization of active substance occurs at site of action.
- Prolongation of drug release.
- Protection of sensitive drugs such as protein and peptides from chemical and enzymatic degradation.

Microspheres are prepared by following methods,

- ✓ Emulsion – solvent evaporation (o/w, w/o, w/o/w)
- ✓ Phase separation (non-solvent addition, and solvent partitioning)
- ✓ Interfacial polymerize
- ✓ Spray drying.

The lactide glycolide homo and copolymers are mostly used for preparation of microspheres, which depending upon variation in copolymer ratio modulates the release.

Spheronization / Pelletization Process

This is one of the newer processes for formulation of oral controlled release dosage forms. Formulation of controlled release pellets, beads or spheres are advantageous than single unit dosage forms. They minimize, dose dumping i.e. unexpected drug release as in case of single unit dosage form. The beads and pellets can be combined to get the multi particulate dosage form which provides customized release profiles. Also incompatible drugs can be delivered by multiparticulate system. Following are the basic methods for pellets or bead production.

a. Microencapsulation
b. Spray congealing
c. Formulation of particles from plastic mass
d. Agglomeration.

Coating Technologies

Coating technology involves the deposition of uniform membrane of polymer onto the surface of the substrates such as tablets, pellets and drug particles. Coating of polymers on substrates provides controlled release using following techniques

a. Film coating
b. Layering coating
c. Compressed coating

Film coating is performed in a coating pan, a fluidized bed or a rotary granulator. Ethyl cellulose, methacrylic ester copolymers, methacryl ester copolymers, cellulose acetate and enteric polymers are used for film coating either alone or in combination.

Factors influencing the design of oral controlled drug delivery systems

The pattern of release of drug from dosage form in the body is dependent on the drug properties. So these properties of drug like physicochemical and physiological must be taken into account before the design of controlled release dosage form.[4]

Physicochemical Factors

Molecular weight of the drug

Diffusivity is the ability of drug to pass through the membrane and is inversely proportional to the molecular size. So the lower the molecular weight faster and more complete is the absorption. Mostly drugs are absorbed through the passive diffusion and the upper limit for passive diffusion is 600 Daltons. So drugs having higher molecular weight are poor candidates for oral controlled release systems. e.g. proteins and peptides.[3]

Dose Size

In controlled release system, the dose is addition of 2-3 doses depending upon objective. That is single dose or twice daily. So the drugs have dose more than 500 mg are unsuitable because the bulk for controlled system will be large.[16]

Aqueous solubility of drug

A drug with good aqueous solubility, especially with pH – independent solubility acts as good candidate for controlled release systems. The aqueous solubility of drug influences the dissolution rate so that controlled release system cannot control the absorption process, so poorly aqueous soluble drugs are poor candidates for controlled release. Since drugs must be in solution form before they are absorbed, drugs with low solubility limit dissolution and suffer bioavailability problems e.g. griseofulvin. Also for drugs having high solubility, it is difficult to reduce dissolution rate and ultimately the absorption.

Drug P^{Ka}

The P^{Ka} range for acidic drugs whose ionization is pH sensitive is 3-7.5 and for basic drugs is 7–11, so for optimum passive absorption the drugs should be non-ionized at site at least to an extent of 0.1 – 5%.

Therefore, drugs which are largely ionized are poor candidate for Controlled Release System.

Partition coefficient

When the drug is ingested, it has to cross many biological membranes for absorption and also for elimination. The ability of drug is to penetrate these lipidic membranes is appearant partition coefficient which is defined as,

$$K = \frac{C_o}{C_w}$$

Where,

K = apparent partition coefficient

C_o = concentration of drug in non-aqueous phase

C_w = concentration of drug in aqueous phase

Drugs with high partition coefficient value easily permeate through biological membrane, but for further functions aqueous solubility is required. So there must be balance between aqueous and oil solubility of drug. This balance gives optimum flux for permeation through biological membranes. Thus, drugs with extreme partition coefficient are undesirable for formulation of controlled release system.

Drug Stability

The stability of drug at site of release and its exposure to bio membrane, influence the design of controlled release system. Drugs that are unstable in stomach pH can be formulated as slow release product, which release the drug only in intestinal environment. Drugs that undergo gut wall metabolism and show instability in small intestine are poor candidate for controlled release system. In such case drug must be chemically modified or other route of administration is preferred.[6]

Protein Binding

The duration of action of drug is function of protein binding. Drug – protein complex serves as sustaining depot for drugs having high protein binding capacity. However, drugs with high protein binding capacity are unsuitable for controlled release system, as they have got long elimination half lives.[5]

Physiological Factors

Absorption

The constant blood or tissue concentration of drug is obtained from controlled release system only when the drug is uniformly released and absorbed. The release rate of drug from dosage form is the rate limiting step rather than absorption and rapid absorption relative to release is essential. So the drugs which are poorly absorbed are poor candidates for controlled release system. The drugs absorbed at special sites of gastrointestinal tract are also poor candidate.

Distribution

For design of controlled release system, all possible information about drug disposition must be known. But decisions are done by considering the some pharmacokinetic parameters, one of which is apparent volume of distribution. Apparent volume of distribution gives the magnitude of drug distribution and protein binding within body. Also it influences the concentration of drug in blood and tissue and elimination kinetics.[6] So, that the drugs having high apparent volume of distribution are poor candidates for controlled release system.

Metabolism

Metabolism of drugs is either an inactivation of active drug or conversion of an inactive drug to active metabolite. The pharmacokinetic parameters like elimination rate constants (Ke) are used to predict the rate and extent of metabolism of drug, so they are considered in design of controlled release system. Following are the two important factors related to metabolism which must be considered during design of controlled release system,

1. For chronic administration, drugs capable of either inducing or inhibiting enzyme synthesis are poor candidates for controlled release system due to difficulty of maintaining uniform blood levels.
2. Drugs undergoing first pass effect or intestinal metabolism are not suitable for design of controlled release system.[6]

Duration of Action

Duration of action significantly affects the design of controlled release system and is dependent on biological half life (t ½).The factors like elimination, metabolism and distribution influence the half life. So, a drug with shorter half life require frequent dosing, making it suitable candidate for controlled release system. But drugs with long half life acts for longer time so they are unsuitable. Drugs with half life less than 2 hrs should not be used because a very large dose will be required

to maintain the release rate. Drugs with half life in range of 2-4 hrs make a good candidate for design of controlled release system.[4]

Side Effects

Due to fluctuations in plasma drug concentration, side effects are developed. The incidences of side effects can be minimized by controlling the concentration within therapeutic range at any given time. Thus, controlled release system reduces the side effects by maintaining the plasma concentration in therapeutic range.

Eg. The gastric irritation caused by drugs like aspirin, potassium chloride reduced due to controlled release.

Margin of Safety

Margin of safety is known by considering the therapeutic Index.

$$T\,I = \frac{TD\,50}{ED\,50}$$

Where,

T I = Therapeutic Index

TD50 = median toxic dose

ED50 = median effective dose

The drug is considered relatively safe, if its TI is more than 1. The drug is considered to be more safer as its TI value increases. TI gives the range of plasma concentration between which drugs are safe and effective. Drugs with narrow therapeutic range require precise control over blood levels of drug so that they are unsuitable for controlled release system.[3,6]

Disease State

In certain cases disease state is important property for considering a drug for controlled release dosage form e.g. aspirin which is not suitable candidate for controlled release dosage Form but its controlled release dosage Form maintain therapeutic concentration particularly over night and thus alleviating morning stiffness in Rheumatoid Arthritis. Also in asthma drug level is maintained for night to avoid bed time or early morning attacks.[3]

Approach for the manufacture of Controlled Release Dosage Form

The importances of controlled drug delivery systems that release bioactive components over extended period of time have been recognized in pharmaceutical field. Of many routes of drug delivery, oral administration is the most convenient and commonly employed means for introduction of drugs to systemic circulation.

For oral delivery of drugs tablet formulation is effective. For tablet formulation direct compression of blends of drugs and additives is the easy method as direct compression technologies entails reduced labour, cost, time operational space and equipment and further no heat or moisture is used so this is preferred method for manufacture of controlled release dosage form.

One of the easy and convenient methods for fabrication of controlled release dosage form is the incorporation of the drug in a matrix containing a hydrophilic, rate controlling polymer e.g. (HPMC, XG) Drug release from such types of systems is controlled by the hydration of polymer, which forms a gelatinous layer at the surface of matrix, through which the included drug diffuses.

Water soluble drugs are released primarily by diffusion of dissolved drug molecules across gel layer, while poorly water – soluble drugs are released predominantly by erosion mechanisms[13]. The hydrophilic matrices show an initial burst of drug release rate due to the release from the surface and the time needed for the formation of an efficient gel layer capable of controlling water penetration and

drug diffusion. This is the case of very soluble drugs and so zero-order release is not obtained and this is the disadvantage of such system.

Materials used for Matrix System

The most widely used materials for matrix system include hydrophilic and hydrophobic polymers. Commonly used hydrophilic polymers are Hydroxy propyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), xanthan gum (XG),(HE C)Hydroxyethyl cellulose ,sodium alginate, poly (ethylene oxide) and cross linked homo polymers and copolymers of acrylic acid. They are usually supplied in micronized forms, as small particle size is critical for rapid gelatinous layer formation on tablet surface.

HPMC is nonionic water soluble cellulose ether. It is available in four different categories based on varying degrees of hydroxyl propyl and methyl substitution namely E,F,J and K series. Xanthan gum is water soluble polysaccharide gum. It is composed of D-glucosyl, D-mannosyl, and D-glucosyluronic acid residues and differing proportions of o-acetyl and pyruvic acid acetal. [5]

Hydrophobic and monolithic polymer matrix systems usually of waxes and water insoluble polymers. e.g. of waxes are carnauba wax, bees wax, candelilla wax, paraffin wax, microcrystalline wax etc. e.g. of insoluble polymers: Eudragit RL 100, RS 100, PO, ethyl cellulose, cellulose acetate, cellulose acetate butyrate etc.

HYPERTENSION

Hypertension is defined as a increasing blood pressure 140/90 mmHg.. Hypertension is a risk factor for myocardial infarction, stroke, congestive heart failure, end-stage renal disease, and peripheral vascular disease. The World Health Organization reported that suboptimal blood pressure (SBP > 115 mmHg) is responsible for 62% of all cerebrovascular diseases and 49% of all ischemic heart diseases. In addition, suboptimal blood pressure is the number one cause of death throughout the Western world.[12]

Clinical classification of hypertension

Although hypertension is rise in blood pressure above the normal clinical values, which can be mild to malignant and therefore classified clinically as summarized below.[13]

Table 1: Clinical classification of hypertension

Category	**Systolic(mm Hg)**	**Diastolic(mm Hg)**
Normal	>130	<85
High Normal	130-139	85-89
Hypertension		
Mild stage(stage1)	140-159	90-99
Moderate(stage2)	160-179	100-109
Severe(stage3)	180-209	110-119
Very sever(stage4)	>210	>120
Malignant hypertension	>200	>140

Figure 3: Activation of renin angiotensin system is shown as follows

Sodium and water retention regulates blood volume and cardiac output. Sodium concentration in the blood is regulated by the release of aldosterone, reduction in glomerular filtration rate and release of atriopeptin hormone from atria of heart.

Decreased release of vasodepressor agents like prostaglandins counters the vasopressor effect of Angiotensin – II.

Endocrinal hypertension is due to a number of endocrinal diseases like adreno cortical hyper function, hyperparathyroidism.

Contraction of aorta causes systolic hypertension due to constriction and diastolic hypertension results from changes in the circulation.

Neurogenic hypertension is due to disease like psychogenic, increase in intracranial pressure.

Antihypertensive agents

Antihypertensive agents are the drugs which lower the blood pressure in hypertensive patients.

Classification of anti hypertensives

1. Diuretics
   e.g. Chlorthalidone, Clopamide, Indapamide
2. β Adrenergic blockers
   e.g. Acebutolol, Atenolol, Metoprolol, Propranolol, Timolol
3. α Adrenergic blockers
   e.g. Terazosin, Prazosin, Doxazosin
4. α + β Adrenergic blockers
   e.g. Labetalol, Carvedilol
5. ACE inhibitors
   e.g. Perindopril, Captopril, Enalapril, Lisinopril, Fosinopril, trandolapril, benazepril etc.
6. Calcium channel blockers
   e.g. Amlodipine, Felodipine, Nifedipine, Nimodipine, Verapamil
7. Vasodilators
   e.g. Hydralazine, Minoxidil, Sodium nitroprusside
8. Angiotension-II receptor antagonists
   e.g. Candesartan, Losartan, Valsartan
9. Central sympatholytics
   e.g. Clonidine, Methyldopa

An overview on Perindopril Erbumine

Numerous studies demonstrated the efficacy of perindopril in the therapy of essential hypertension. Perindopril doses of 4 to 16 mg administered once daily are more effective than placebo in the treatment of mild-to-moderate hypertension. Doses greater than 8 mg offer no advantage in most patients; however, in some patients doses of 12 or 16 mg daily provide greater therapeutic benefit. The antihypertensive activity of perindopril is linear at doses up to 8 mg, with 2 mg doses having only slight antihypertensive activity. Administration with hydrochlorothiazide, indapamide, and nifedipine in patients demonstrating an inadequate response to monotherapy has resulted in improved blood pressure control.

The long-term efficacy of perindopril was reported in the results of an open trial evaluating 690 patients. Therapy was initiated with perindopril 4 mg once daily and increased, if necessary, to 8 mg. If diastolic blood pressure remained greater than 90 mmHg on perindopril 8 mg, a diuretic was added, then another antihypertensive agent was added if necessary. After 1 year of therapy systolic and diastolic blood pressure were reduced by 29 mmHg and 19 mmHg, respectively. Perindopril monotherapy normalized blood pressure in 55% of the patients. Blood pressure control was achieved in 78% of the patients. After 3 years, perindopril monotherapy at 4 or 8 mg controlled blood pressure in 56% of the patients.[13]

The efficacy of perindopril was demonstrated in several studies enrolling elderly patients with essential hypertension. Perindopril doses of 2 to 8 mg daily reduced systolic and diastolic blood pressure. In a double-blind study enrolling 34 patients with a mean age of 84 years, perindopril reduced systolic pressure 10% and diastolic pressure 9%. Blood pressure control (defined as blood pressure < 160/95 mmHg) was achieved in 92.5% of patients (62.5% at the dosage of 2 mg per day, 22.5% at 4 mg per day, 7.5% at 8 mg per day, and 5% at 8 mg per day plus 40 mg nifedipine). The efficacy of perindopril was evaluated in 2,927 elderly patients (≥70 years) in an open study. At initiation of therapy with perindopril 2 or 4 mg once daily, diastolic blood pressure was between 94 and 115 mmHg. After 1 or 3 months

of therapy, the dose could be doubled or a diuretic added if the perindopril dose had reached 8 mg in patients with diastolic blood pressure remaining above 90 mmHg. Diastolic blood pressure was reduced to less than 90 mmHg in 69% of patients at 1 month, 86% of patients at 3 months (in patients on perindopril alone), and 94% at 6 months. At 6 months, diastolic blood pressure was lowered 28 mmHg and systolic blood pressure 16.6 mmHg.

The efficacy of perindopril was demonstrated in several groups of patients with hypertension and concomitant disease including hyperlipidemia, Type II diabetes, ischemic heart disease, cardiac arrhythmia, peripheral arterial occlusive disease, nephropathy with proteinuria, and chronic obstructive pulmonary disease. Efficacy was demonstrated in patients with hypertension receiving nonsteroidal anti-inflammatory agents (indomethacin or diclofenac). In all groups, perindopril 4 mg once daily effectively reduced blood pressure without negatively affecting the patient's concomitant disease state or therapy. Perindopril did not affect lipid or apolipo protein levels in patients with hyperlipidemia, did not affect glucose control in diabetic patients, had an anti-ischemic and anti anginal effect in those with ischemic heart disease, and reduced urinary albumin excretion in patients with proteinuria. Other studies have shown a lack of effect of perindopril on lipid or carbohydrate metabolism. Several studies demonstrated the safety and efficacy of perindopril in the treatment of hypertension in patients with diabetes or glucose intolerance. Perindopril has not negatively affected glucose tolerance, insulin sensitivity, renal function, or lipid profiles in diabetic patients treated long-term.[14]

2. LITERATURE REVIEW

- **Jignesh P. Prajapati *et al.,*** developed absorption factor method and validated for the simultaneous determination of perindopril erbumine and amlodipine besylate in their combined pharmaceutical formulation dosage form. Absorption factor method was performed for perindopril erbumine and amlodipine besylate at wavelength maxima 216nm and 237nm respectively. Result of analysis was validated by statistically. The result of the studies showed that the proposed Spectroscopic method is simple, rapid, precise and accurate.

- **SB. Bhanja, P. Ellaiah *et al.,*** developed and optimized a sublingual tablet of Perindopril which is an effective drug in the treatment of hypertension. Perindopril containing tablets were prepared by direct compression method using different ingredients such as Crospovidone, Sodium saccharin, Mannitol, Microcrystalline cellulose, Talc and Magnesium stearate. The tablets were evaluated for physical properties including Hardness, Weight variation, Thickness, Friability, Drug content, Wetting time, Water absorption ratio, *In-vitro* disintegration time, *In-vitro* dissolution study and also Drug release kinetic study.

- **Mukesh C. Gohel *et al.,*** fabricated modified release tablet of metoprolol succinate using hydroxypropyl methylcellulose (HPMC) and xanthan gum as a matrixing agent. The *in vitro* drug dissolution study was carried out in pH 6.8 phosphate buffer employing paddle rotated at 50 rpm. It was concluded that the desired drug release pattern can be obtained by using a proper combination of HPMC (high gelling ability) and xanthan gum (quick gelling tendency). The matrix integrity during dissolution testing was maintained by using hydroxyl propyl methylcellulose.

- **Murthy. P.N. V. N *et al.,*** prepared controlled-release matrix tablets of Guaiphenesin and Salbutamol Sulphate and evaluated by using Na CMC, Xanthan gum, HPMC100cps, Ethyl Cellulose (15cps), Compritol, Precirol in different concentrations for treatment of respiratory disorders. The manufacturing procedure was optimized with respect to the thickness between 6.3 to 6.5mm, hardness 5 to 6 kg/cm^2 and description being white, oval shaped tablets with break line on one side. Formulation containing NaCMC, Xanthan gum, HPMC100cps polymers showed higher rate of drug release over a period of 24hrs.

- **Masadi Rajukar *et al.,*** formulated the oral controlled release Trimtazidine di hydrochloride tablets by using HPMC and Xanthan gum as rate controlling polymer. The tablets were prepared by direct compression method. Drug content in formulation was determined by UV Method. The *in vitro* release study of matrix tablets were carried out in 0.1N Hydrochloric acid with pH 1.2 for 10 hours. It was observed that the amount of polymer influences the drug release.

- **P. Subash Chandra Bose *et al.,*** described about the buccal region which was attractive route for systemic drug delivery. Perindopril was an ACE inhibitor widely used as an hypertensive agent shows less oral bioavailability as it undergrows first pass metabolism. Perindopril patches were prepared using HPMC K4M, Chitosin, HPMCP, PVP and PVA. *In vitro* release studies were conducted for perindopril loaded patches in 6.6 p^H phosphate buffer solution. Buccoadhesive patches of perindopril can be developed as potential controlled release formulation for the treatment of hypertension.

- **Mridanga raj ray *et al.,*** have studied about the powders which were evaluated for angle of repose, bulk density and tapped density whereas the prepared tablets were evaluated for weight variation, thickness, diameter, hardness, friability, drug content and *in vitro* release study.

- **Talukdar and Mooter *et al.,***have investigated the properties of xanthan gum matrix tablet *invivo*. They have used poorly water soluble and highly water soluble drugs for study. They have done single oral dose pharmacokinetic study according to randomized crossover design in six healthy male volunteers. There was no statistically significant difference in time to reach the C_{max} and AUC. But maximal plasma concentration was varied considerably. They concluded that, although the common pharmacokinetic parameters of the drug from test products were not significantly different from the marketed product, the therapeutic efficacy of drug from former may be superior to that of latter.

- **Talukdar and RenaltKinget *et al.,*** have done the comparative study on xanthan gum and HPMC as matrices for controlled release drug delivery. They have concluded that drug diffusion in hydrated HPMC matrices is higher than in hydrated xanthan gum matrices. This showed that xanthan gum has higher ability than HPMC to retard the release of drug when used as matrix forming agent.

- **Kranz *et al.,*** studied the drug release mechanism from HPMC matrices and developed a new model for quantitative predictions of controlled drug delivery.

- **Tao Yi *et al.,*** worked on controlled release for poorly soluble drug from solid self-micro emulsifying formulations with high viscosity hydroxyl propylmethylcellulose and they concluded that possibility of combining the characteristics of controlled release and self-emulsifying formulations for the biopharmaceutical requirements of oral poorly water-soluble drugs.

- **Ford and Velasco *et al.,*** studied the influence of drug (HPMC) (Hydroxy methyl propyl cellulose) ratio and other technological factors such as drug and polymer particle size and compression force on the drug release from the matrices of HPMC. The influence was assessed by multi way analysis of variance. They reported that release from HPMC ratio. The particle size also influenced the release to lesser extent and the compression force didn't affect the release parameters.

- **JamzadShahla *et al.,*** worked on development of a controlled release low dose class II drug by using HPMC and they found that HPMC matrices showed a significantly greater degree of hydration and swelling and stronger texture property relative to PEO matrices. Results indicated that in the case of low dose/low soluble drug, total drug release in a zero order manner heavily depends on the synchronization of erosion and swelling fronts during the entire dissolution study.

- **VermaRajan K, Garg Sanjay *et al.,*** worked on selection of excipients for extended release formulations of glipizide through drug–excipients compatibility testing and they reported results of DSC along with IR and/or HPLC were successfully employed to assess the compatibility of glipizide with the excipients used in the development of extended release formulations.

- **Basak SC *et al.,*** prepared propranolol hydrochloride matrix tablets with hydroxypropyl methylcellulose polymer to control the release of drug with a view to develop twice daily sustained release dosage form. The resulting matrix tablets prepared with hydroxyl propyl methyl cellulose K4M fulfilled all the official requirements of tablet dosage forms. The *in vitro* drug release was measured in aqueous solutions for a total period of 12 h using 1.2 pH bufferfor first 1 h and pH 7.5 buffer for the rest of period. The drug release was within the limits of predetermined set USP requirements.

- **Kenneth I. Ozoemenaa *et al.,*** described about enantio selective, potentiometric membrane electrodes based on carbon-paste impregnated with and cyclodextrin as chiral selectors for the assay of *S*-perindopril is described. Response characteristics showed that the proposed electrodes could be reliably applied in the assay of *S*-perindopril raw material and its pharmaceutical formulation. The best enantio selectivity and time-stability were exhibited by cyclodextrin based electrodes.

- **Yeole PG *et al.,*** made an attempt to increase therapeutic efficacy, reduce frequency of administration, and improve patient compliance, by developing sustained release matrix tablets of diclofenac sodium. Sustained release matrix tablets of diclofenac sodium, were developed by using different drug: polymer ratios, such as F1 (1:0.12), F2 (1:0.16), F3 (1:0.20), F4 (1:0.24) and F5 (1:0.28). Xanthan gum was used as matrix former, and microcrystalline cellulose as diluent. All the lubricated formulations were compressed using 8 mm flat faced punches. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness, *in vitro* dissolution using basket method, and swelling index.

- **NevinErk *et al.,*** developed a new sensitive, simple, rapid and precise reversed-phase high performance liquid chromatographic (HPLC) and two spectrophotometric methods to resolve binary mixture of Perindopril and indapamide in the pharmaceutical dosage forms. The first method is based on HPLC on a reversed-phase column using a mobile phase of phosphate buffer pH 2.4 and acetonitrile (7:3 % v/v) was used. Linearity range for Perindopril and indapamide was 5.0–70.0 and 8.0–35.0 g/ ml. In the second method, the first derivative Spectrophotometry with a zero-crossing technique of measurement is used for the simultaneous quantitative determination of Perindopril and indapamide in binary mixtures without previous separation step.

- **K S Lakshmi.** ***et al.***., validated HPTLC method for simultaneous determination of losartan and perindopril in tablets. A simple, controlled and precise high performance thin layer chromatographic method has been developed for the simultaneous determination of losartan and perindopril in tablet. Separation was carried out on pre-coated TLC plates, coated with silica gel 60 F 254. The separation was done by using a mobile phase toluene: acetonitrile: formic acid (5:5:0.3%v/v/v). After development, the chromatographic plates were scanned at 215 nm. The R_f value of losartan and perindopril was found to be 0.55 and 0.27 respectively. The results of the analysis have been validated statistically and by recovery studies.

- **Raja sekharan*etal.,*** was developed formulation and evaluation of theophylline controlled released matrix tablets using antham gum. Controlled release matrix tablets of theophylline were prepared with hydrophilic polymer xantham gum and evaluated. Controlled release matrix tablets of theophylline were prepared by wet granulation technique by varying polymer ratios (1:1 and 1:2) and hardness (5,6 and 7 kg/cm^2). IR spectroscopy revealed that there was no interaction between the drug and the polymer used in the formulation. *In vitro* dissolution studies were performed using Disso 2000 (Paddle type). From this study it was proved that the release of theophylline from matrix tablets was influenced by both polymer ratio and hardness.

- **BhanjaSatyabrata *et al.,*** designed and carried out *in vitro* evaluation of mucoadhesive buccal tablets of perindopril prepared by sintering technique to avoid the first pass metabolism and to improve its bioavailability with reduction in dose and also dose related side effects. The half-life of perindopril is approximately 0.8 to 1 hrs. The tablets were prepared by direct compression method containing polymer polyethylene oxide and carnauba wax. The prepared tablets were sintered at various temperatures like 60^0 c and 70^0c for 1.5 hr and 3 hr. The *in vitro* release of perindopril was performed under sink conditions (phosphate buffer ph 6.8, at 37 ± 0.5^0c and 50 rpm) using usp-xxiv dissolution apparatus.

- **Thawatchai Phaechamud *et al..,*** formulated controlled release of propranolol hcl from chitosan-lactose-xanthan gum matrix tablets. The application of low molecular weight materials chitosan as matrix component for controlled propranolol HCL release prepared by direct compression was studied. The effect of the additives on drug release from matrix tablets containing chitosan was investigated an incorporation of xanthan gum into chitosan tablet could prolong the drug release rather than that containing single polymer. The drug release could be modified by addition of lactose. The drug release was gradually enhanced as the greater amount of the lactose was added into the matrix. Most of drug dissolution profiles could be well fitted with first order kinetic release.

- **Hisham E. Abdellatef *et al.,*** described about Simple, rapid, accurate and sensitive spectrophotometric methods for the determination of perindopril. The coloured products are measured spectrophotometrically at 588, 843, 419, 550 and 520nm for DDQ, TCNQ, TCNE, CL and *p*-CA, respectively, optimization of different experimental conditions is described. Beer's law is obeyed in the range of 20–200mg/ml and colours were produced in non-aqueous media and were stable for at least 1hr. Application of the suggested methods to perindopril tablets are presented.

- **J. Siepmanna *et al.,*** studied the modeling of drug release from delivery systems based on HPMC.

- **M.HarishShoaib *et al.,*** Evaluated drug release from ibuprofen matrix tablets using HPMC.

- **Antesh K jha *et al.,*** studied the formulation and *in vitro* evaluation of sustained release matrix tablets of metoprolol succinate using hydrophilic polymers.

- **Bishyajit Kumar biswas *et al.,*** studied the *in vitro* release kinetics study of esomeprazole magnesium from methocel K15M and methocel K100M matrix tablets.

- **Roshanpradhan *et al.,*** studied the HPMC (HPMC- K4M, K15M and K100M) matrix tablets containing indomethacin, the release character of matrix tablets were investigated in the intestinal fluid 6.8 p^H phosphate buffer for 12 hours.

3. AIM AND OBJECTIVE

The aim of the present work was to formulate and evaluate controlled release matrix tablets of Perindopril Erbumine by using polymers like Xanthan gum, HPMC K100 M.

Perindopril Erbumine is an anti hypertensive drug having low molecular weight (368.46g/ml), short biological life (1.2hr), suggests it is an ideal candidate for controlled drug delivery system which offers advantages like reduce frequency of administration, better patient compliance and better controlled release profile. Perindipril erbumine was effective in small doses (2 to 16 mg). Hence it was used in hypertension and congestive cardiac failure.

Natural and synthetic polymers was designed for controlled release as they are bio compatible, non toxic and better patient tolerance.

So, in present study planned to formulate Perindopril Erbumine as controlled release matrix tablets formulation.

To study the effect of drug, polymer ratio in release rate.

To study the rate of drug release and mechanism of drug release from designed formulation.

4. PLAN OF WORK

The present study was proposed to carry out in the following phases for formulation and evaluation of controlled release matrix tablets of Perindopril Erbumine.

Phase-I

- Pre-formulation study of pure drug
- Compatibility study
    - Fourier transform infrared spectroscopy (FT-IR)
- Preparation of standard curve of Perindopril Erbumine
    - In acid buffer(pH 1.2)
    - In phosphate buffer (pH 6.8)

Phase-II

Formulation and evaluation of controlled release matrix tablets of Perindopril Erbumine

- Formulation of Perindopril Erbumine matrix tablets
- Evaluation of Perindopril Erbumine matrix tablets
    - Physical evaluation
    - Drug content study
    - *In vitro* Dissolution study
    - Kinetic data analysis

Phase-III

Accelerated stability studies.

5. DRUG PROFILE

5.1 PERINDOPRIL ERBUMINE

Perindopril Erbumine is a dipeptide monoacid monoester with a perhydroindole group and no sulphydryl radical; chemical name, tert-butyl ammonium (2S, 3aS, 7aS)-1-(N-[(S)-1-ethoxycarbonyl butyl]-L-alanyl) perhydroindole-2-carboxylate and used for the treatment of patients with hypertension and symptomatic heart failure.

Physical and chemical properties

Empirical Formula	**:**	$C_{19}H_{32}N_2O_{5,}C_4H_{11}N$
Molecularweight	**:**	368.46 g/mol
Meltingpoint	**:**	126°-128°C
Category	**:**	Antihypertensive
Description	**:**	White crystalline powder, slightly hygroscopic odourless, bitter in taste.

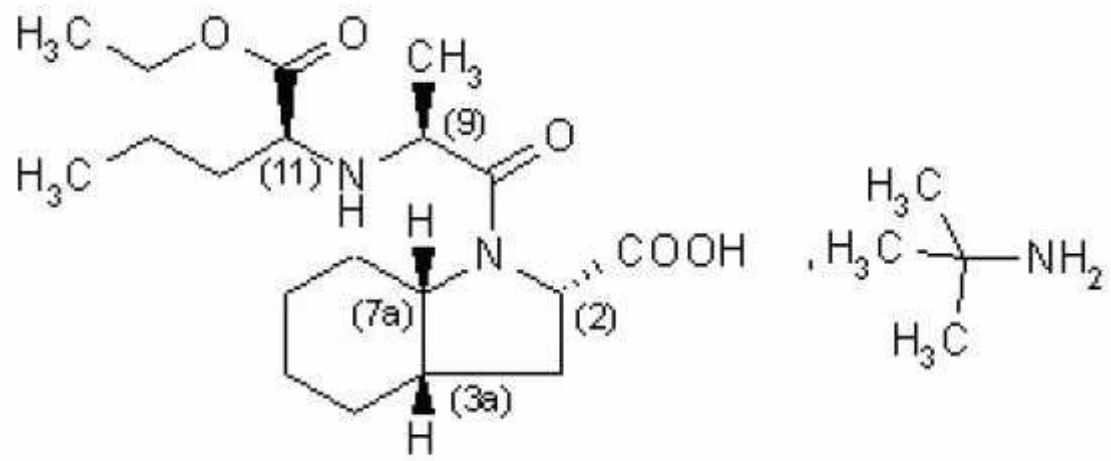
Solubility

The Perindopril erbumine is soluble in water, methanol, ethanol, acetic acid and ethyl acetate, slightly soluble in ether, chloroform and benzene.

Chemical Nature

Perindopril erbumine dipeptide monoacid monoester with a per hydroindole group and no sulphydryl radical.

Structure



Structure of Perindopril Erbumine

Chemical name: *Tert-butylammonium (2S, 3aS, 7aS)-1-(N-[(S)-1-ethoxycarbonyl butyl]-L-alanyl) perhydroindole-2-carboxylate*

Pharmacokinetics

Absorption **:** Well absorbed after oral administration.

Route of administration **:** Oral

Protien Binding **:** 10 - 20%

Bioavailability **:** 65% - 75 %

Metabolism **:** Hepatic

Half life **:** 1.2 hr

Excretion **:** Renal

Volume of Distribution **:** Approx. 140-160L/kg

Clearance **:** 219 – 362 m/min.

Dissociation Constant (P^{ka}) **:** 2.6

Elimination Half-life **:** 0.8-1 hr

Mechanism of Action

Perindopril erbumine inhibits ACE in human subjects and animals, while the principle mechanism of perindopril is blood pressure reduction is believed to be through the renin-angiotension- aldoserone system.

ACE inhibitors such as Perindopril cause lower blood pressure by inhibiting angiotensin-converting enzyme (ACE), which is important for the formation of angiotensin II. Perindopril inhibit the formation of angiotensin II from angiotensin I. So, in blood decreases the levels of angiotensin II. Normally the Angiotensin II would cause constriction of arteries and elevation of blood pressure so its inhibition will relax the arteries and lower blood pressure, and improve the cardiac pumping efficiency and output in patients with heart failure.

Adverse effects

Hypotension, tachycardia, chest pain, palpitations, hyperkalaemia, skin rashes, non-productive cough, headache.

Contraindications

Diuretics reduce the bioavailability of perindopril erbumine, Pregnancy contraindicated.

Interactions

Perindopril Erbumine is known to interact with other drugs like Fluorouracil, Lithium, Phenobarbitone, Phenytoin (Na), Warfarin (Na), Digoxin, Azathioprine, Aspirin. These interactions are sometimes beneficial and sometimes may pose threats to life.

Indications

The drug is effective in the treatment of Hypotension, Anaphylactic reactions during desensitization, membrane exposure, Intestinal angioedema, Neutropenia.

Dosage

Adult dose: 4-8 mg as a single dose for 1 day.

Commercial dosage

Aceon 4mg (Solvey pharma.)

Conversyl 4mg (Aurobindo Pharma)

Warnings / Precautions

Alcoholic drinks and alcohol containing medicines should be avoided during Perindopril Erbumine treatment. Do not administer to subjects with a history of blood dyscrasia.

Specification **:** 4mg

Storage **:** Protect from direct light.

Shelf life **:** 24 months.

Package

Tablets × 1 blister in PVC/aluminum blister packaging.

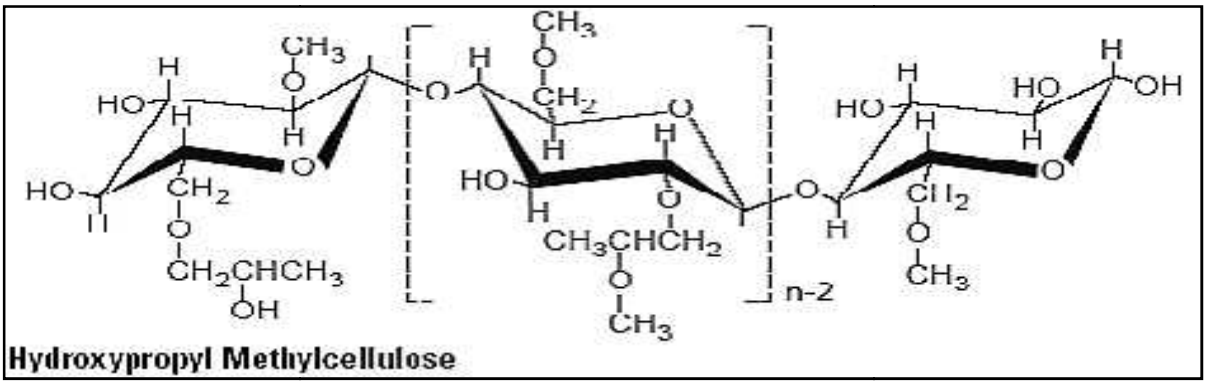
5.2 EXCIPIENTS PROFILE

HYDROXY PROPYL METHYL CELLULOSE. (HPMC)[20, 22]

Synonyms: Cellulose, hydroxyl propyl methyl ether, HPMC, methocel, metolose

Chemical Formula: HPMC is a partially o-methylated and o-(2-hydroxy propylated) cellulose. It is available in several grades, vary in viscosity and extent of substitution

Structural Formula of HPMC K100M



Solubility

Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol, and ether, but soluble in mixture of ethanol and dichloromethane, and mixture of methanol and dichloromethane

Molecular Weight **:** 100 – 150000

Description

HPMC is an odorless and tasteless, white or creamy white colored fibrous or granular powder

Functional Category

Coating agent, film-former, stabilizing agent, suspending agent, tablet binder, and viscosity increasing agent

Stability and Storage Conditions

HPMC is a stable material although it is hygroscopic after drying. Solutions are stable between pH 3-11. Increasing temperature reduces the viscosity of solutions. It undergoes a reversible sol to gel transformation upon heating and cooling respectively. Stored in a well closed container, in a cool, dry place

Incompatibilities

It is incompatible with some oxidizing agent. Since it is nonionic, it will not complex with metallic salts and ionic organics to form insoluble precipitates

Safety

It is generally regarded as a nontoxic and non-irritant material although excessive oral consumption may have a laxative effect

Applications

HPMC is widely used in oral and topical pharmaceutical formulations. In oral products it is primarily used as a tablet binder, film coating and as an extended release tablet matrix. Concentration between 2-5% w/w may be used as a binder either in wet or in dry granulation process. High viscosity grades may be used to retard the release of water soluble drugs from a matrix. Lower viscosity grades are used in aqueous film coating while higher viscosity grades are used with organic solvents.

XANTHAN GUM [21,22]

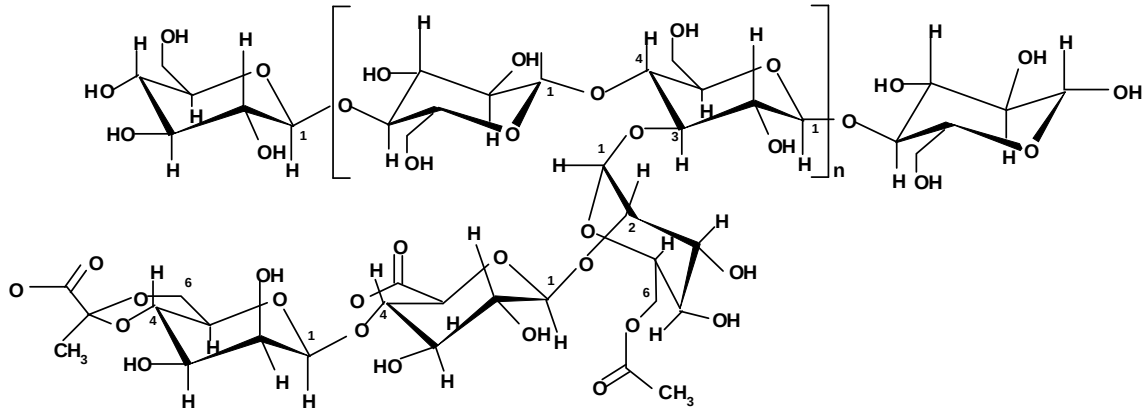
Chemical name **:** Xanthan gum

Empirical formula **:** $(C_{35}H_{49}O_{29})_n$

Molecular weight **: (**933) $_n$ Daltons

Chemical Structure

Chemical Structure of Xanthan Gum



Xanthan is an anionic bacterial polysaccharide composed of a U-(1→)-D-Gle(1→)-beta-D-GLC (cellulosic) backbone with a tri saccharide side chain linked to C_3 of every second glucose residue.

The side chain is U-D-Man-(1→)-U-D-Gle A-1(/→2)-6-O-acetyl-alpha-D-Man-(1/→beta-D-Glca-((1→2)-alpha-D with approximately 60% of the terminal mannose units being pyruvylated and 90% of the proximal mannose units substituted at C_6 with O-acetyl groups. It has side chains of 2 mannose and 1 gluconic glucoronic acid group.

Xanthan gum is an exo cellular polysaccharide reduced by fermentation of the bacteria *Xantho monascam pestris.*

Description

Xanthan gum is off white granular powder. In cold water, it is dispersed to form pseudo plastic mixtures. It is highly water soluble.

Melting point: 270 °C

Viscosity (dynamic):1200–1600 mPas (1200-1600 cP) for 1% w/v aqueous solution at 25°C.

Salt solutions: Compatible and stable in solutions with high salt concentrations.

Others

It has unique enzyme resistance. Upon heating it may increase or maintain viscosity. It is affected by shear but recovers hence, is thixotropic gelling agent. It stabilizes solid, liquid, and gaseous dispersions, viscosity dispersions are highly pseudoplastic, Xanthan exhibits pseudo plasticity on the basis of its helical structure.

Stability and Storage

Xanthan gum is a stable material Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60°C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Solutions are also stable in the presence of enzymes, salts, acids, and bases.

Applications in pharmaceutical formulation or technology

Gum provides visibly clear solutions even at higher concentrations; it exhibits less gummy mouth-feel than gums with more Newtonian characteristics. Xanthan gum is commercially available in both clarified and non clarified forms. Clarified Xanthan gives visibly clear solutions even at high concentrations, while unclarified xanthan gums are opaque. It acts as an emulsion stabilizer, holds water, enhances freeze-thaw stability, inhibits starch retro gradation improves shelf-life and serves to bring about stabilization dispersions, suspension, and emulsion, and

thickeners. Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets. Controlled-release tablets of diltiazem hydrochloride prepared using xanthangum have been reported to sustain the drug release in a predictable manner and the drug release profiles of these tablets were not affected by pH and agitation rate.[22]

MAGNESIUM STEARATE [21, 23]

Synonym: Magnesium octadecanoate, octadecanoic acid, magnesium salt.

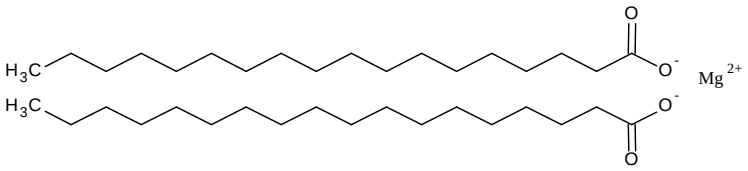
Chemical Name: Octadecanoic acid magnesium salt.

Empirical Formula: $C_{36}H_{70}MgO_4$

Structural Formula

$[CH_3 (CH_2)_{16}COO]_2Mg$

Structural Formula of Magnesium stearate



Molecular Weight

591.34

Melting Point

117-150 °C (commercial samples); 126-130 °C (high purity)

Solubility

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Description

Magnesium stearate is a very fine, light, white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Typical Properties

Crystalline forms **:** High-purity magnesium stearate has been isolated as a tri hydrate, a di hydrate, and an anhydrate.

Density (bulk) **:** 0.159 g/cm^3

Density (tapped) **:** 0.286 g/cm^3

Density (true) **:** 1.092 g/cm^3

Flow ability **:** Poorly flowing, cohesive powder.

Melting range **:** 117–150^{0}C (commercial samples)

Solubility **:** Practically insoluble in ethanol, ether and water; slightly soluble in warm benzene and warm ethanol.

Specific surface area **:** 1.6–14.8 m^2/g

Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and Pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Functional Category

Tablet and capsule lubricant.

Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well closed container in a cool, dry place.

Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being non toxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

TALC [21, 23]

Synonyms

Hydrous magnesium calcium silicate, hydrous, magnesium silicate, magnesium hydrogen meta silicate, powdered talc, Purtalc, soap stone, steatite.

Chemical Name

Talc

Structural Formula

$Mg_6 (Si_2O_5)_4(OH)_4$

Empirical Formula

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6 (Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

Molecular Weight

379.27 g

Solubility

Talc is practically insoluble in dilute acids and alkalis, organic solvents, and water.

Description

Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Typical Properties

Moisture content : Talc absorbs insignificant amounts of water at 258^0C and relative humidity's up to about 90%.

Particle size distribution : Varies with the source and grade of material.

Refractive index : n_D^{20} = 1.54–1.59

Solubility : Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Specific gravity : 2.7–2.8

Specific surface area : 2.41–2.42m^2/g

Storage Conditions : Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities : Incompatible with quaternary ammonium compounds.

Applications in Pharmaceutical Formulation or Technology

Talc is used in oral solid dosage formulations as a glidant and lubricant (1-10%) and diluent (5-30%), as a dissolution retardant in the development of controlled-release products, as an adsorbent, as a dusting powder in topical preparations (90-99%).

Functional Category

It is used as an anti caking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

Storage Conditions

Talc should be stored in a well-closed container in a cool, dry place.

Safety

Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially non-toxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs.

POLYVINYL PYRROLIDONE [20, 21]

Synonym

Povidone, polyvinyl pyrrolidone, PVP, kollidone, and plasdone

Chemical formula

1-ethenyl-2-pyrrolidinone homopolymer. $(C_6H_9NO)_n$

Molecular weight

2500-3000000

Description

It is white to creamy white, odourless or almost odourless, hygroscopic powder

Functional category

Tablet binder, suspending or viscosity increasing agent

Solubility

Readily soluble in water, organic solvents including monohydric (ethanol, methanol) and polyhydric alcohols, acids, esters, ketones, and chloroform

Stability and storage conditions

Aqueous solutions are susceptible to growth of molds and consequently required the addition of suitable preservatives.

Incompatibility

It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds

Safety

Chemically, PVP is inert and nontoxic. It does not irritate the mucous membrane of rabbit eyes, antigenic property and does not interfere in antibody formation studies.

Applications

Carrier for drug, dispensing agent, suspending or viscosity builder, tablet binder, tablet diluents and coating agent.

MICRO CRYSTALLINE CELLULOSE

Synonym

Avicel PH; Cellets; Celex; Hellulosum micro cristallinum, MCC Sanaq.

Molecular weight : 36000

Empirical formula : $C_6H_{10}O_5$

Functional category

Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

Solubility

Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids and most organic solvents.

Stability and storage conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well closed container in a cool place and dry place.

Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

6. MATERIALS AND METHODS

6.1.1 LIST OF MATERIALS

List of materials and equipments were used for the formulation and evaluation given in table no 2 and 3

Table no 2: materials and their suppliers

S. No.	Materials	Source
1.	Perindopril Erbumine	AurobindoPharma Limited, Hyd
2.	Xanthan gum	S.d. Fine chemicals limited, Mumbai
3.	HPMCK100M	S.d. Fine chemicals Chemicals, Mumbai
4.	MCC	S.d. Fine chemicals limited, Mumbai
5.	PVP	S.d. Fine chemicals limited, Mumbai
6.	Talc	S.d. Fine chemicals limited, Mumbai
7.	Magnesium stearate	S.d. Fine chemicals limited, Mumbai

6.1.2 LIST OF EQUIPMENTS

Table 3: Equipments and their Manufacturer

S. No	Name of the Equipment	Supplier / Manufacturer
1.	Electronic balance	Shimadzu BL-2204
2.	Hot air oven	Spencers
3.	Tablet compression machine	Kimya engineers
4.	Tablet Dissolution tester USP XXII	Lab India
5.	Disintegration apparatus	Campbell electronics, Mumbai.
6.	Friability test apparatus	Roche Friabilator.
7.	pH meter	Systronics, Mumbai.
8.	UV-Visible Spectrophotometer	Lab India 3000.
9.	Hardness tester	Monsanto
10.	Blender tester	Konark instruments.Ambala,Haryana.
11.	Rotary Shaker	Konark instruments.Ambala,Haryana.
12.	FTIR Spectrophotometer	Bruker Alpha.

6.2 PRE-FORMULATION STUDIES

Pre-formulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the pre-formulation phase begins early in the discovery process such the appropriate physical, chemical data is available to aid the selection of new chemical entities that enter the development process during this evaluation possible interaction with various inert ingredients intended for use in final dosage form are also considered in the present study.

The following pre-formulation studies were performed

- ✓ Study of organoleptic properties
- ✓ Solubility analysis
- ✓ Melting point of drug
- ✓ Drug powder characterization
- ✓ Drug-excipients compatibility study by FT-IR[24]

6.2.1 Organoleptic properties

The Organoleptic character of the drug like colour, odour, taste and appearance play an important role in the identification of the sample and hence they should be recorded in an descriptive terminology.

6.2.2 Solubility studies

It is important to know about solubility characteristics of a drug in aqueous systems, since they must possess some limited aqueous solubility to elicit a therapeutic response. Quantitative determination of solubility was made by preparing saturated solution of drug in a constant volume of water, methanol, ethanol, acetic acid and ethyl acetate and resulting solutions were kept at room temperature for 24 hours with intermediate shaking.

6.2.3 Melting point

The melting point of Perindopril Erbumine was determined by capillary method. The small quantity of Perindopril Erbumine was placed in apparatus and the melting point was determined which was matched with standards.

6.2.4 Loss on drying

Determination was done on 1.000 g of sample by drying it in an oven at 100°C to 105°C for 3 hours.

Accurately weighed the substance to be tested. If the sample was in the form of large crystals, reduced the particle size to about 2 mm by quickly crushing. A glass stopper, shallow weighing bottle that had been dried for 30 minutes under the same conditions to be employed in the determination were taken. The sample was taken in bottle and replaced with the cover. The bottle with the contents was accurately weighed. The sample was evenly distributed practicable to a depth of about 5 mm by gentle and sidewise shaking. The loaded bottle was placed in the drying chamber. The sample was dried at the specified temperature until a constant weight was reached. Upon opening the chamber, the bottle was closed promptly and allowed to come to room temperature in desiccators before weighing.

The difference between successive weights should not be more than 0.5mg. The loss on drying was calculated by the formula

$$\% \text{ LOD} = \frac{(W_2 - W_3)}{(W_2 - W_1)} \times 100$$

Where, W_1 = Weight of empty weighed bottle

W_2 = Weight of weighed bottle + sample

W_3 = Weight of weighed bottle + dried sample

6.2.5 Drug powder characterization[25]

6.2.5.1 Angle of repose

Angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles. The internal angle between the surface of the pile and horizontal surface is known as the angle of repose and is related to the density, surface area and co-efficient of friction of the raw material.

Method

Angle of repose was determined by using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed blend was allowed to pass through the funnel freely on the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\Theta = \tan^{-1} (h/r)$$

Where, h = height of heap, r = radius of heap, Θ = angle of repose.

Table 4: Angle of repose limits

Angle of repose	Flow property
$<25^{o}$	Excellent
$25\text{-}30^{o}$	Good
$30\text{-}40^{o}$	Passable
$>40^{o}$	Very poor

6.2.5.2 Bulk density

Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape as the particle become more spherical in shape, bulk density increase. In addition as the granule size increases bulk density decreases.

It is the ratio between a given mass of a powder and it's bulk volume

Bulk Density = Bulk Mass / Bulk Volume

Method

A given quantity of the power was transferred to a measuring cylinder and tapped mechanically either manually or using some tapping device till a constant volume is obtained. This volume is the bulk volume (v) and it includes the true volume of the powder and the void space among the powder particles. A given peak of powder has air spaces between the particles .This air space called void space or void volume.

6.2.5.3 Tapped density

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder. Then the tapping was done and the tapped volume was noted. The tapped density was calculated by using the following formulae

$$\text{Tapped Density} = \frac{m}{Vf}$$

Where, m = initial weight of material in gm,

Vf = volume of material after tapping.

6.2.5.4 Measurement of powder compressibility[26]

The compressibility Index and Hausner's ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing powder, bulk density and tapped density have closer values as such interactions are generally less. For poorer flowing materials, there are frequently greater inter particle interactions and hence, a greater difference between bulk and tapped densities was observed. These differences are reflected in the compressibility Index and the Hausner's ratio calculated by the formula

$$\text{Compressibility index: } = 100\frac{(V_0 - Vf)}{V_0}$$

Where,

V_f = final tapped volume,

V_0 = initial untapped volume.

Table 5: Limits of Compressibility index

S.no	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	>40	Extremely poor

$$\text{Hausner's ratio} = \frac{V_0}{Vf}$$

Where, Vf = final tapped volume, Vo = initial un tapped volume.

Table 6: Limits of Hausner's ratio

S. no	Hausner's ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

6.3 Drug-Excipient Compatability Studies

Fourier Transform Infrared (FTIR) Spectroscopy

FT-IR spectra of pure drug, Pure HPMC K100 M, Pure Xanthan Gum & physical mixtures of this polymer with drug were recorded on Bruker alphaFT-IR spectrophotometer using KBr discs. The instrument was operated under dry air purge and the scans were collected at scanning speed 2 mm/sec with resolution of 4 cm^{-1} over the region 4000-400 cm^{-1}. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction.

6.4 Construction of calibration curve

6.4.1 Calibrations curve of Perindopril Erbumine in Acid buffer pH 1.2

Preparation of 0.2 M potassium chloride

0.2 M Potassium Chloride was prepared according to IP 1996. A quantity of 14.9 gm of potassium chloride was dissolved in water and made up the volume to 1000 ml using water.

Preparation of 0.2M HCl

0.2 M HCl prepared by diluting 17ml of Conc. HCl in to water and made up the volume to 1000ml using water.

Preparation of Acid buffer pH 1.2

The Acid buffer pH 1.2 prepared according to IP 1996 by mixing the 50ml of 0.2 M potassium chloride and 85 ml of 0.2 M HCl and made up the volume to 200ml using water.

Scanning of Perindopril Erbumine in Acid buffer pH 1.2

The absorption maxima of the standard solution were scanned between 200-400 nm on Lab India 3000 UV-Vissible spectrophotometer. The absorption maxima were found at 216 nm.

Procedure

An accurately weighed quantity of Perindopril Erbumine was dissolved in an amount of methanol not exceeding 2% of final volume and diluted quantitatively with Acid buffer pH 1.2 to obtain a solution having known concentration(4, 8, 12, 16, 20, 24, 28 and 32 µg/ml). Absorbance of Perindopril Erbumine determined at 216 nm.

6.4.2 Calibration curve of Perindopril Erbumine in phosphate buffer pH 6.8

Preparation of 0.2 M potassium dihydrogen phosphate

0.2 M potassium dihydrogen phosphate was prepared according to IP 1996. A quantity of 27.2 grams of potassium dihydrogen phosphate was dissolved in water and made up the volume to 1000ml using water.

Preparation of 0.2 M NaOH

0.2 M NaOH prepared by dissolving 8 gms of NaOH in to water and made up the volume to 1000ml using water.

Preparation of phosphate buffer pH 6.8

The phosphate buffer pH 6.4 prepared according to IP 1996 by mixing the 50ml of 0.2 M potassium dihydrogen phosphate and 39.1ml of 0.2 M NaOH and make up the volume to 200ml using water.

Scanning of Perindopril Erbumine in phosphate buffer pH 6.8

The absorption maxima of the standard solution were scanned between 200-400 nm on Lab India 3000 UV-Vissible spectrophotometer. The absorption maxima were found to 216 nm.

Procedure

An accurately weighed quantity of Perindopril Erbumine was dissolved in phosphate buffer pH 6.8 to obtain a solution having known concentration (4, 8, 12, 16, 20, 24, 28 and 32 µg/ml). Then absorbance of Perindopril Erbumine was determined at 216 nm.

6.5 Formulation of controlled release matrix tablets of Perindopril Erbumine by direct compression method

The key ingredients included in the formulation are

Hydrophilic polymers: Xanthan gum and HPMC K100M
Filler : MCC
Anti adherent : Talc
Lubricant : Magnesium Stearate
Binder : PVP

Accurately weighed quantities of polymer and MCC were taken in a mortar and mixed geometrically to this required quantity of Perindopril Erbumine was added and mixed with the help of pestle. The powder blend was then lubricated with magnesium stearate and talc mixed for about 3 minutes.

Compression operation was carried on rotary tablet compression machine fitted with 6 mm round shaped, standard flat face punch sets having plain on both sides at average weight 100 mg/tab.

Before going to compression powder blend was evaluated for all physical parameters like angle of repose, bulk density, tapped density, carr's index, hausner's ratio.

Formula of Controlled release matrix tablets of Perindopril Erbumine

Table 7: Formulation of Perindopril Erbumine controlled release matrix tablet

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Perindopril Erbumine	4	4	4	4	4	4	4	4	4
HPMC K100M	30	35	40	-	-	-	15	20	20
Xanthan gum	-	-	-	30	35	40	20	15	20
PVP	5	5	5	5	5	5	5	5	5
MCC	59	54	49	59	54	49	54	54	49
Talc	1	1	1	1	1	1	1	1	1
Mg. stearate	1	1	1	1	1	1	1	1	1
Total wt(mg)	100	100	100	100	100	100	100	100	100

6.6 Evaluation of controlled release tablets of Perindopril Erbumine

6.6.1 Tablet thickness and diameter

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using vernier callipers.

6.6.2 Hardness

This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this six tablets were selected at random and the hardness of each tablet is measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

6.6.3 Friability

The friability test was carried out to evaluate the hardness and stability instantly in Roche Friabilator. Here twenty tablets were weighed (Wo) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations i.e., 25 rpm for 4 minutes, the tablets were again weighed (w). The percent loss in weight or friability (F) is calculated by the formula

$$F= (1-W/Wo) \times 100$$

F= friability

Wo= initial weight

6.6.4 Weight variation

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range. This was done by sampling randomly and weighing 20 tablets and average weight was calculated. Not more

than two of the individual weights deviate from the average weight by more than the percentage show in the table 8 and none deviate by more than twice the percentage The mean and standard deviation were determined**.**

Table 8: Pharmacopoeial specifications for tablet weight variation

Average weight of tablets (mg) (I.P)	**Average weight of tablets (mg) (U.S.P)**	**± % deviation allowed**
Less than 80	Less than 130	10
80 – 250	130 – 323	7.5
More than 250	More than 324	5

6.6.5 Content uniformity

This test was performed to maintain the uniformity of weight of active ingredient in each tablet which should be in the prescribed range according to the Indian Pharmacopoeia. This test was performed by taking twenty tablets randomly, weighed and powdered. A quantity of powdered tablet equal to 100 mg of perindopril Erbumine is dissolved in 0.1 N HCL in 100ml volumetric flask. It is diluted and the absorbance is measured at 224 nm using 0.1 N HCL as blank and the % drug content was estimated using the following formula.

$$\text{Concentration (mcg/ ml)} = \frac{\text{Absorbance-intercept}}{\text{Slope}}$$

Drug content (mg) = concentration x dilution factor

$$\% \text{ Drug content} = \frac{\text{Drug content (mg)}}{\text{Label claim (mg)}} \times 100$$

6.6.6 *In vitro* dissolution studies

Dissolution studies were carried out by using USP II dissolution apparatus. The stirring speed was 50 rpm. It was maintained at 37 ± 1˚C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid wherever necessary and were analyzed at 216 nm by using a double beam UV spectrophotometer. Each dissolution study is performed three times and the mean values were taken.

Details of dissolution test

Dissolution test apparatus	: USP TYPE II
Speed	: 50 rpm
Stirrer	: Paddle type
Volume of medium	: 900 ml
Aliquot taken at each time interval	: 5 ml
Medium used	: pH 1.2 acid buffer for 2 hrs. And pH 6.8 phosphate buffer for 22 hr
Temperature	: 37 ± 0.5 ^{0}C

6.7 Release kinetic study

The rate and mechanism of release of Perindopril Erbumine through the prepared controlled release matrix tablets were analyzed by fitting the drug release data into

Zero order equation

$$Q = Q_0 – K_0 t$$

In this equation Q is the amount of drug remaining undissolved at time t, Q_0 is the amount of drug undissolved at t = 0 and K_0 is the corresponding release rate constant.

First order release equation

$$\ln Q = \ln Q_0 – K1t$$

Where M is the amount of drug undissolved at time t, Q_0 is the amount of drug undissolved at t = 0 and K1 is the corresponding release rate constant.

Higuchi Square Root Law equation

$$Q = K2t0.5$$

Where Q (Q = 100 - M) is the amount of drug dissolved at time t and K2 is the diffusion

The Korsmeyer - peppas equation

$$Mt / M_\infty = K\ tn$$

Where Mt / M_∞ is the fraction of drug released at time t, K is the Korsmeyer release rate constant and n characterizes the mechanism of drug release from formulations during diffusion process. If n = 0.45 it is case I or Fickian diffusion, 0.45, n, 0.89 is for anomalous diffusion or non- Fickian transport, n = 0.89 for case II transport, n .0.89 for super case II transport.

From Korsemeyerspeppas model,

- ✓ The value of n falls between 0.5 to 1 (0.5 < n <1) indicating non-fickian release.
- ✓ The value of n =0.5 indicating Fickian diffusion i.e. first order release
- ✓ The value of n = 1, indicating the Zero order release or case 2 transport
- ✓ The value of n >1, indicating the Super case 2 transport

6.8 Stability protocol

The purpose of stability testing is to provide evidence on how the quality of a drug substances or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a re-testing for the drug substances or a shelf-life for the drug product and recommended storage conditions.

The storage conditions used for stability studies were accelerated conditions (40°C±2°C/75%±5% RH). Stability study was carried out for the optimized formulation. Tablets of optimized formulation were packed in strips and kept in stability chamber for 3 months on above mention temperature.

The samples were kept at 40°C±2°C/75%±5% RH and analysed for weight variation, hardness, friability, drug content and *in vitro* dissolution study for every month for a period of 3 months.

7. RESULTS AND DISCUSSION

7.1 PRE-FORMULATION STUDIES

7.1.1 Appearance

The sample of Perindopril Erbumine was white or almost white, odourless or almost odourless crystalline powder.

7.1.2 Solubility

The Perindopril Erbumine was soluble in water, methanol, ethanol, acetic acid and ethyl acetate, very slightly soluble in ether, chloroform and benzene.

7.1.3 Melting point

The melting point was found to be 126°-128°C.

7.1.4 Physical characteristics of drug

Table No 12: Physical characteristics of drug (Perindopril Erbumine)

S. No	Parameter	Specifications
1	Loss on Drying (%)	0.40
2	Bulk density (g/ml)	0.415
3	Tapped Density (g/ml)	0.498
4	Hausner's ratio	1.26
4	Compressibility index (%)	<15
5	Angle of repose (° ')	24.11°

All the powder characteristics were good and satisfied according to pharmacopeia.

7.2 FTIR Studies

Potential chemical interactions between the drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibilities of chemical interaction between drug and excipients. FTIR spectra of pure drug and optimized formulations were analyzed over the range 400-4000cm^{-1}. Compatibility studies were performed using FT-IR Spectrophotometer. The FT-IR spectrum of pure Perindopril Erbumine drug was compared with FT-IR spectrum of physical mixture of Perindopril Erbumine (Perindopril Erbumine, HPMC K100 M, Xanthan gum, MCC, PVP, Talc and Mg.sterate). The spectra for all formulations are shown below figure no 4 to 9.

Figure No 4: FTIR spectra of Perindopril Erbumine

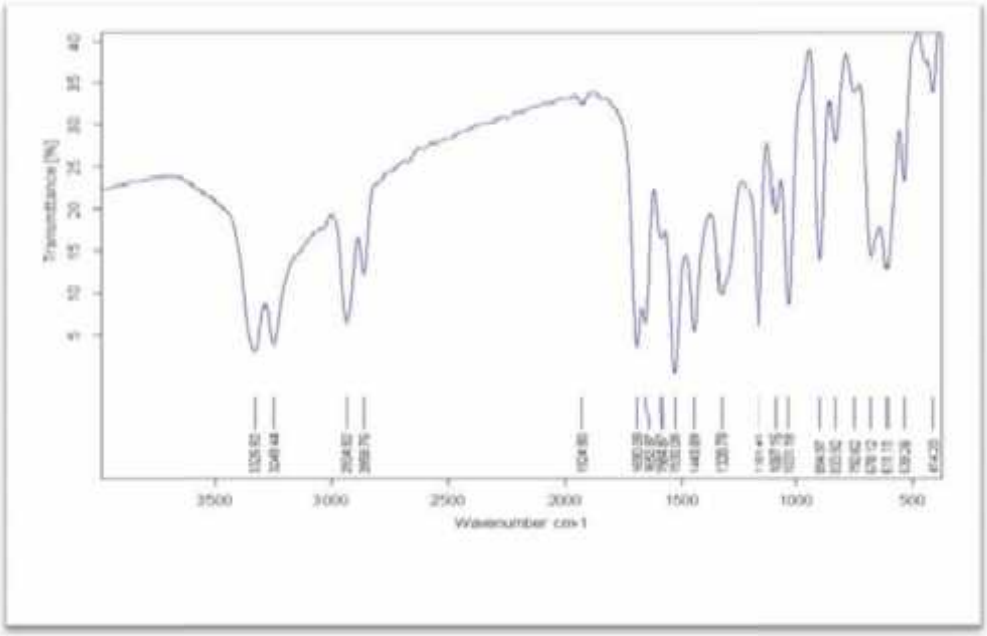


Figure No 5: FTIR spectra of Xanthan gum

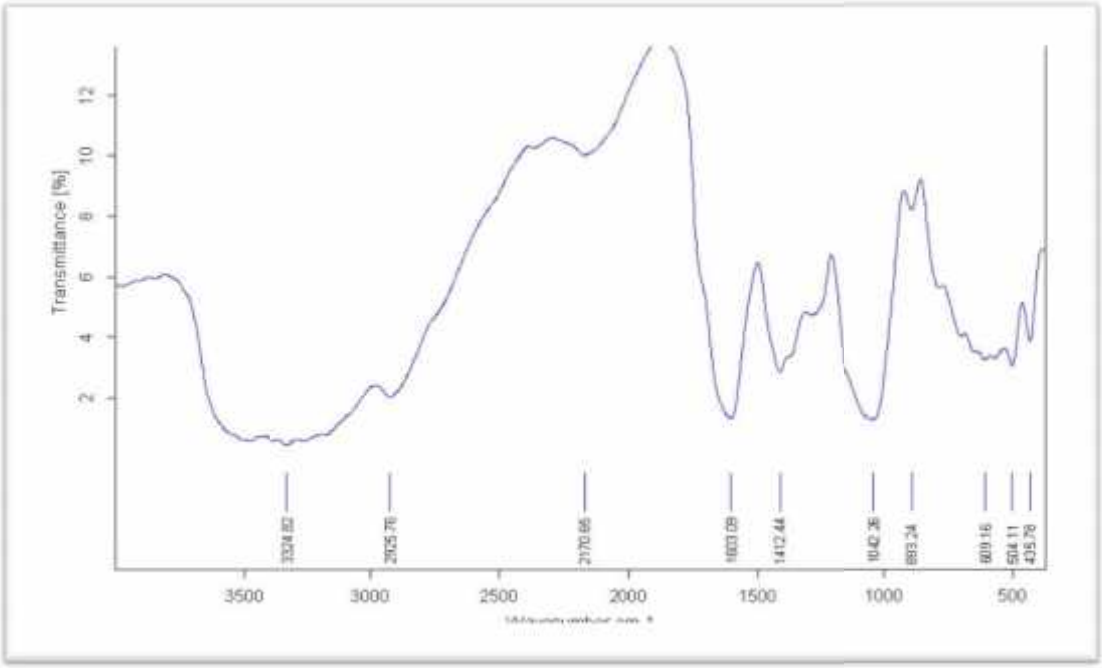


Figure No 6: FTIR spectra of HPMC

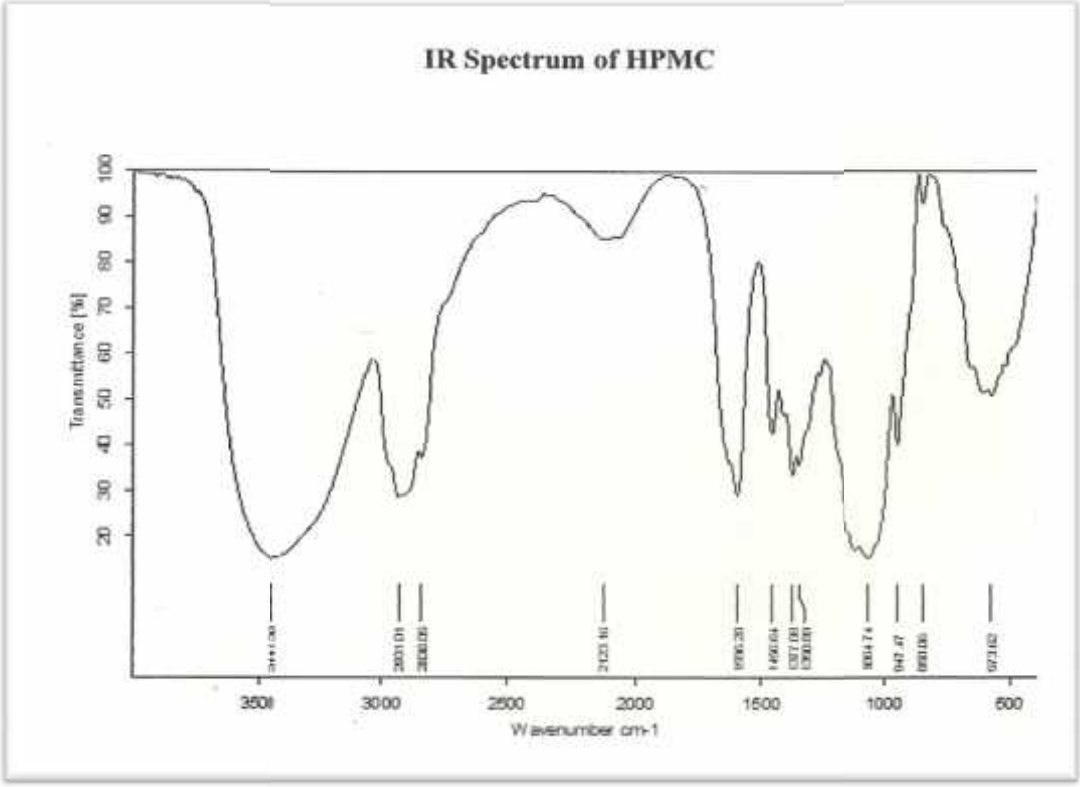


Figure No 7: FTIR spectra of Magnesium stearate

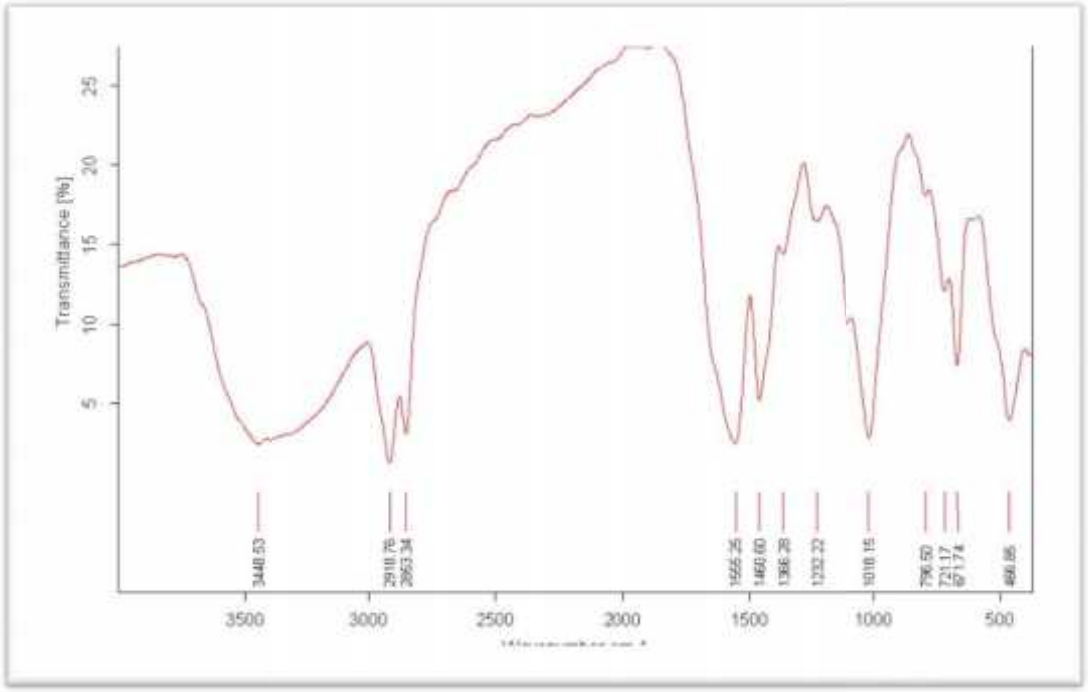
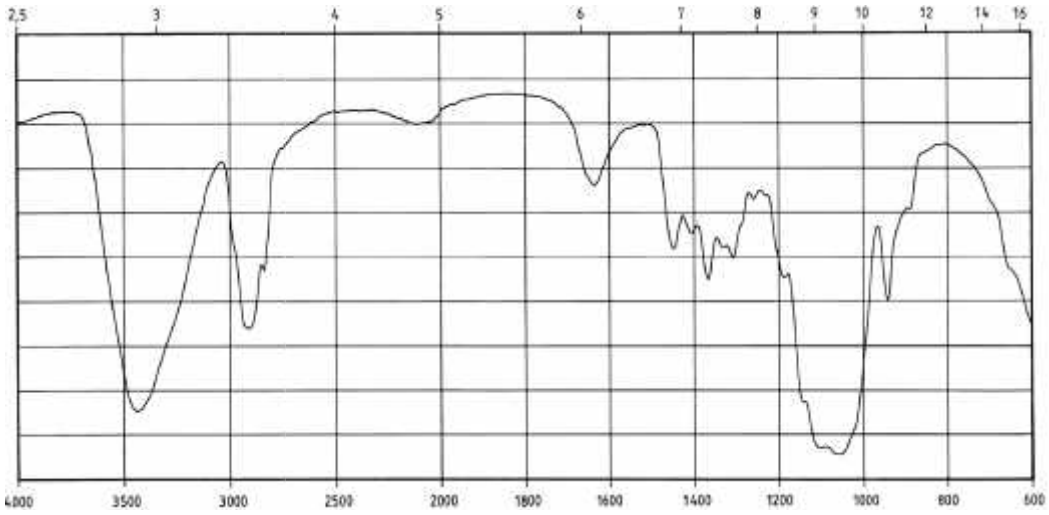
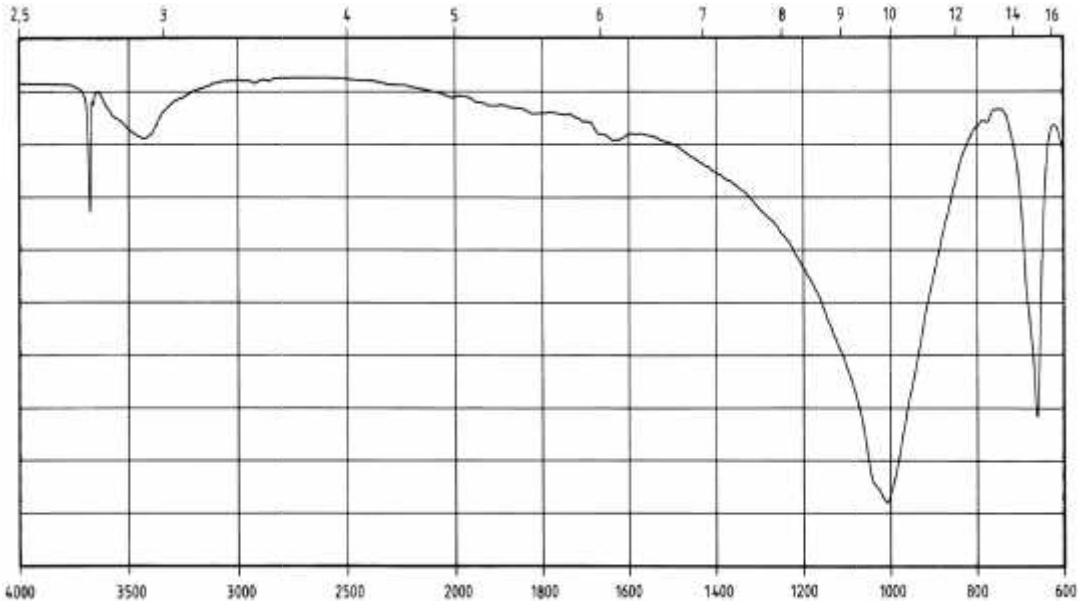


Figure No 8: FTIR spectra of MCC



Wave number ($^{cm-1}$)

Figure No 9: FTIR spectra of Talc



Wave number ($^{cm-1}$)

Figure No 10: FTIR spectra of Drug with excipients

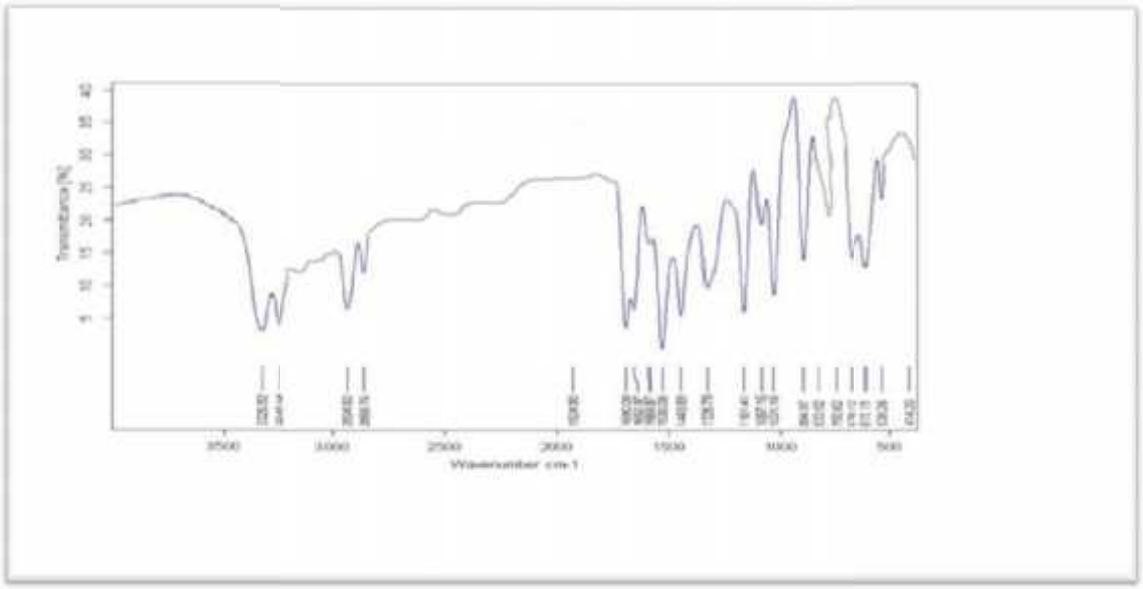


Table No 10: FT-IR Peaks of various compounds

Wave number in cm^{-1}	**Functional groups**	**Pure drug perindopril erbumine**	**Physical mixture**
1210-1150	C-N Stretching	1151.2 cm^{-1}	1152.4 cm^{-1}
1360-1180	C-NH_2 Stretching	1306.1 cm^{-1}	1307.5 cm^{-1}
1900-1600	C=O Stretching	1800.8 cm^{-1}	1800.8 cm^{-1}
2990-2850	C-CH_3 Stretching	2984.9 cm^{-1}	2983.2 cm^{-1}
3490-3300	N-H Stretching	3305.9 cm^{-1}	3306.7 cm^{-1}

The FTIR spectrum analysis showed that there is no appearance or disappearance of any characteristic peaks of pure perindopril erbumine and in the physical mixture of drug with polymer and excipients. The presence of peaks at the expected range confirms that the materials taken for the study are genuine. The results were showed in table no 10.

Due to stretching C-N, C-NH_2, C=O, C-CH_3 and N-H respectively in optimized formulations also these peaks were well preserved with additional peaks which correspond to the excipients used in the formulation. This indicated that no drug excipients interaction.

7.3 Calibration curve of Perindopril Erbumine

Calibration curve of Perindopril Erbumine was determined in pH 1.2 acid buffer, by plotting absorbance versus concentration (µg/ml) at 216 nm and by using concentration at range of 4-32 µg/ml and the following result was obtained.

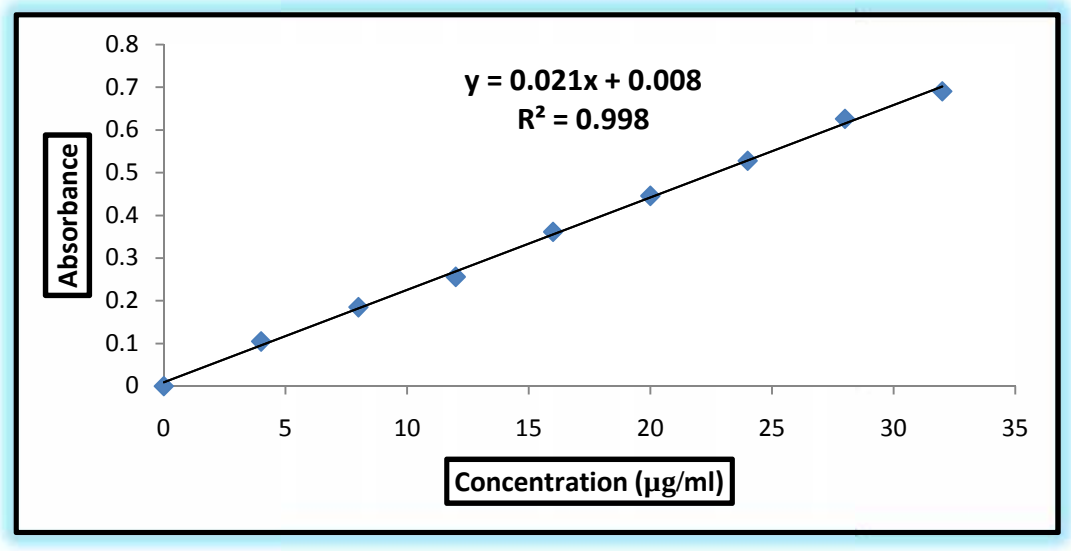
A. In pH 1.2 Acid buffers

The calibration curve of the Perindopril erbumine was prepared by using pH 1.2 acid buffer.

Table No 11: Data for calibration curve of Perindopril erbumine in Acid buffer pH 1.2

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	4	0.10458
3	8	0.18481
4	12	0.25583
5	16	0.36112
6	20	0.44562
7	24	0.52758
8	28	0.62594
9	32	0.69025

Figure No 11:Calibration curve Graph in pH 1.2 Acid Buffer



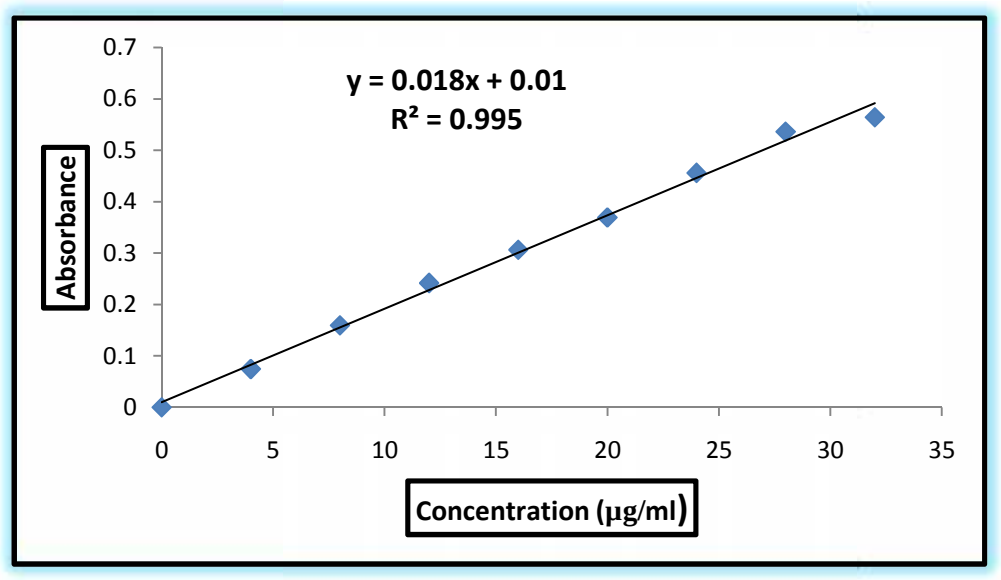
B. In pH 6.8 Phosphate Buffer

The calibration curve of the Perindopril erbumine was prepared in the Phosphate buffer pH 6.8.

Table No 12: Data for calibration curve of Perindopril erbumine in phosphate buffer pH 6.8

S.NO.	Concentration(µg/ml)	Absorbance
1	0	0
2	4	0.07442
3	8	0.15916
4	12	0.24156
5	16	0.30596
6	20	0.36892
7	24	0.45565
8	28	0.53568
9	32	0.56364

Figure No 12: Calibration curve Graph in PH 6.8 Phoshphate Buffer.



7.4 Evaluation of pre compression parameters

Table No 13: Powder characterization of formulations

Formulation code	Angle of repose (± SD)	BD (gm/ml) (± SD)	TD (gm/ml) (± SD)	Carr's index (%) (± SD)	Hausner's ratio (± SD)
F1	23.03±0.04	0.412±0.02	0.477±0.02	14.92±0.05	1.18±0.05
F2	20.85±0.01	0.407±0.03	0.486±0.01	14.91±0.07	1.19±0.04
F3	20.85±0.04	0.410±0.06	0.481±0.01	13.93±0.04	1.21±0.02
F4	22.30±0.07	0.398±0.04	0.491±0.07	14.72±0.01	1.19±0.06
F5	19.98±0.09	0.396±0.03	0.480±0.03	13.12±0.03	1.16±0.03
F6	22.06±0.06	0.412±0.01	0.489±0.01	14.27±0.01	1.15±0.01
F7	23.19±0.03	0.409±0.04	0.472±0.02	13.56±0.04	1.16±0.03
F8	22.05±0.09	0.401±0.05	0.492±0.03	12.91±0.07	1.17±0.05
F9	24.11±0.03	0.415±0.01	0.498±0.04	15.00±0.06	1.26±0.04

(n=3±S.D) (S.D=Standard deviation)

For the powder blend of all the formulated batches, the angle of repose was found to be in the range of 19° to 24°, thus indicating that the flow properties were excellent. Hausner's ratio was less than 1.20 for all the batches indicating good flow properties.

7.5 Evaluation of Perindopril Erbumine tablets

The results were showed in table no 14.

Table No 14: Evaluation of Physical Characteristics of controlled release matrix tablets of Perindopril Erbumine

Formulation code	Weight variation(mg) (±SD)	Hardness (kg/cm^2) (±SD)	Thickness (mm) (± SD)	Drug content (mg) (± SD	Friability %
F1	100.4±1.24	4.93±0.23	3.009±0.02	93.76±0.19	0.30
F2	100.9±1.61	4.13±0.30	3.009±0.02	98.16±0.27	0.40
F3	100.4±1.56	3.73±0.11	3.008±0.02	89.87±0.41	0.16
F4	100.3±1.28	3.93±0.23	3.009±0.02	97.28±0.33	0.40
F5	100.8±1.16	4.13±0.15	3.008±0.02	93.48±0.26	0.60
F6	100.0±1.42	4.4±0.2	3.010±0.0	95.67±0.17	0.60
F7	100.8±1.00	4.0±0.2	3.009±0.02	93.87±0.32	0.50
F8	100.8±1.28	3.53±0.11	3.009±0.02	88.92±0.21	0.51
F9	100.3±1.04	4.0±0.115	3.009±0.02	97.87±0.16	0.57

(n=3±S.D) (S.D=Standard deviation)

The histograms of hardness, thickness, weight variation, friability and drug content was mentioned in figure no 13 to 16.

Figure No 13: Thickness and Hardness of Perindopril Erbumine tablets

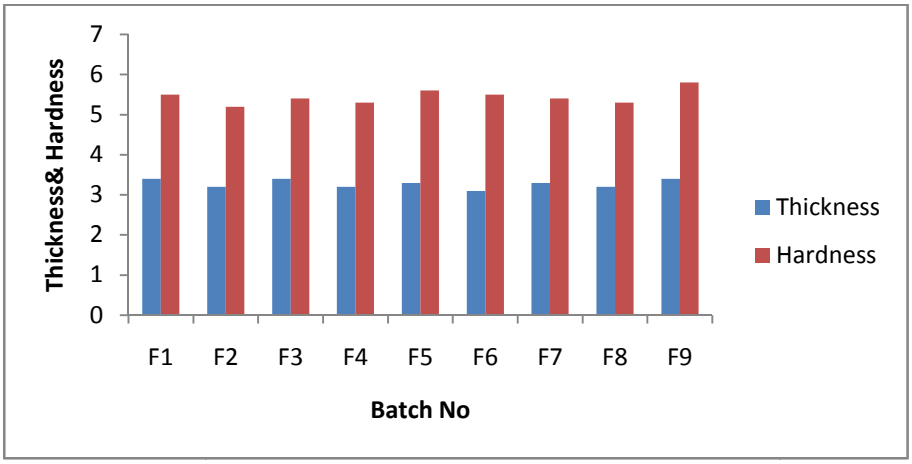


Figure No 14: Friability of Perindopril Erbumine tablets

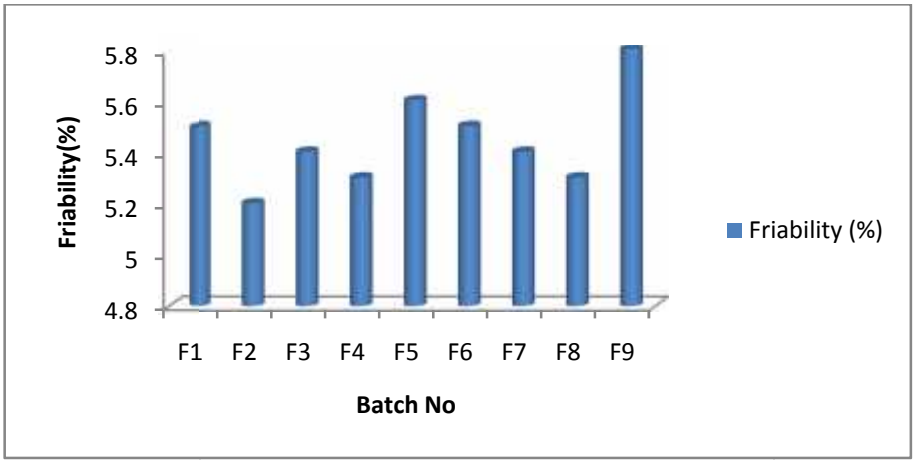


Figure No 15: Weight variation of Perindopril Erbumine tablets

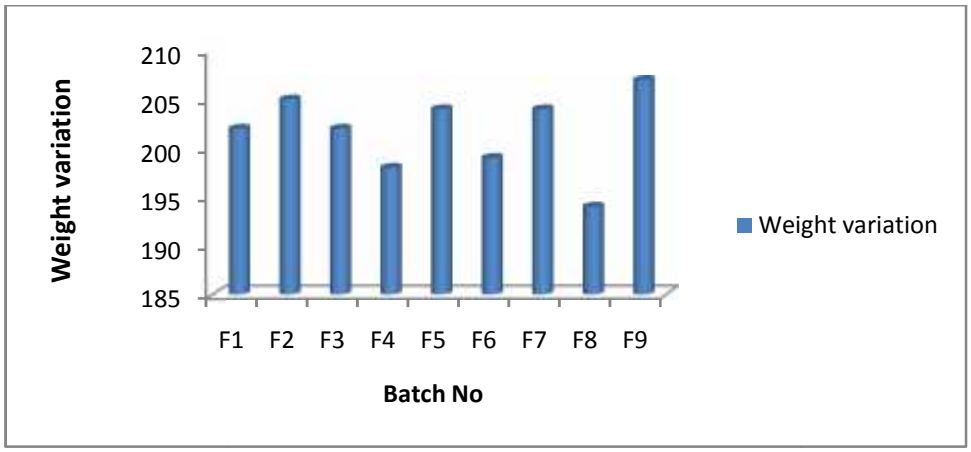
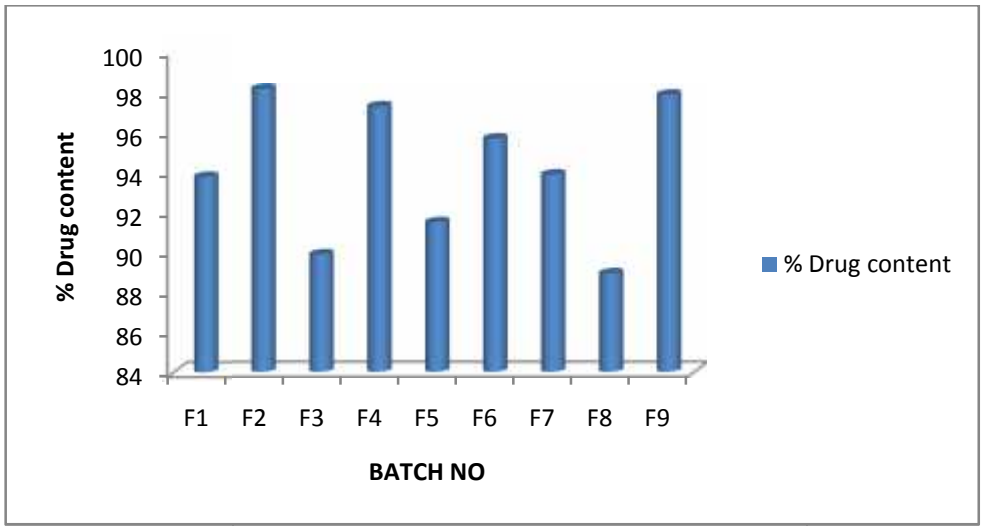


Figure No 16: % Drug Content of Perindopril Erbumine tablets



- The weight variations for all the formulation F1 to F9 were within the pharmacopoeial specification.
- Thickness of all the formulations F_1 to F_9 was in the range of 3.008-3.010 mm.
- Hardness of all the formulations F_1 to F_9 was in the range of 3.53- 4.13 kg/cm^2.
- Diameter of all the formulations F_1 to F_9 was in the range of 6.008-6.010 mm.
- Friability of all the formulations F_1 to F_9 was in the range of 0.16% to 0.60%
- Drug content all the formulations F_1 to F_9 was in the range of 93 to 100%.

All the prepared formulations were tested for physical parameters like Hardness, Thickness, Weight variation, Friability, were found to be within pharmacopoeial limits. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that prepared formulations were good.

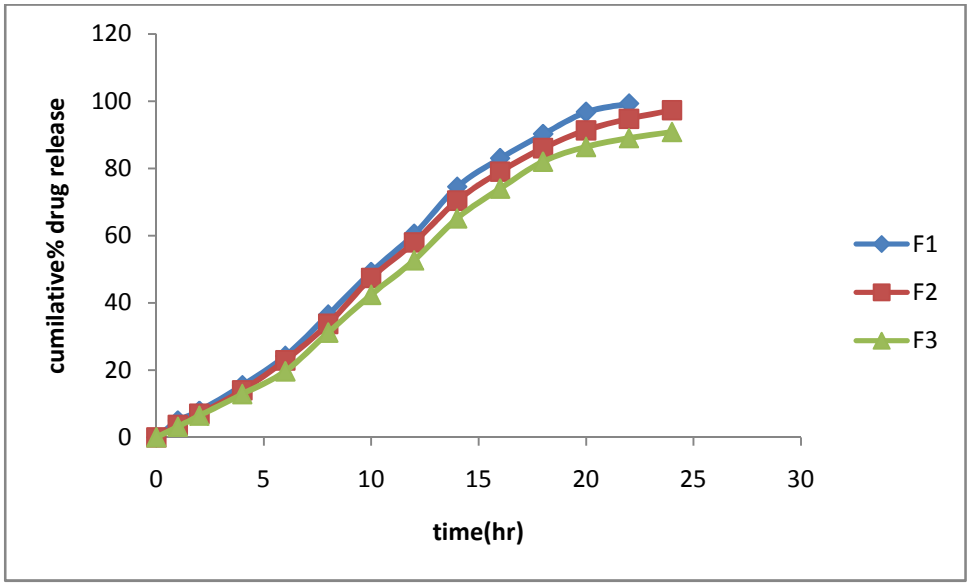
7.6 *INVITRO* DRUG RELEASE STUDY

The dissolution studies of the formulation (F_1 to F_9) were carried out in USP dissolution apparatus (paddle) in 900 ml of 0.1N HCL of pH 1.2 for 2 hr and phosphate buffer pH 6.8 for remained 22 hr as dissolution medium. The reports are represented in the tables no 15 to 17 and Fig 17 to 19 respectively. The results of dissolution study was depends on polymer concentration.

Table No 15: Cumulative Percentage drug release of formulations with HPMC K100M (F_1-F_3)

Time(hr)	Cumulative % drug release F_1	Cumulative % drug release F_2	Cumulative % drug release F_3
0	0	0	0
1	4.98	3.64	3.15
2	7.86	6.99	6.42
4	15.46	13.98	12.87
6	24.19	22.89	19.65
8	36.47	33.75	31.16
10	49.19	47.39	42.41
12	60.46	57.97	52.65
14	74.49	70.38	65.11
16	83.78	79.13	74.42
18	90.19	86.72	82.21
20	96.74	91.31	86.41
22	99.24	94.74	89.63
24	-	97.27	90.81

Figure No 17: Cumulative percentage drug release of formulations containing HPMC K100 M

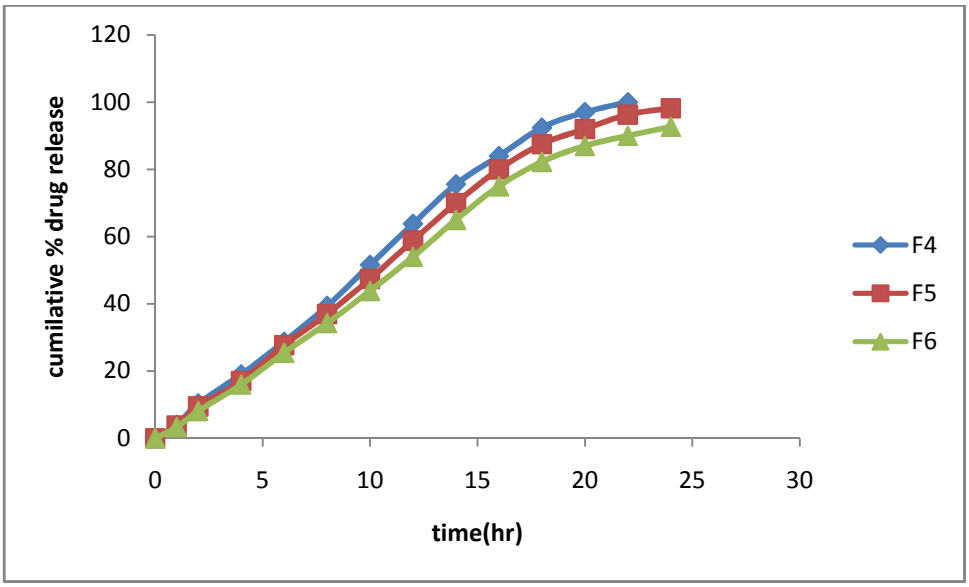


From the above figure no 17 it can be observed that the polymer HPMC K100 M has controlled effect on the release of drug from the controlled release matrix tablet. The percentage of drug release from formulations F_1, F_2 and F_3 were 99.24%, 97.27% and 90.81% respectively and difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer. The cumulative percent of drug release from various formulations and release coefficients values of the various models for respective formulation were represented in table no 15.

Table No 16: Cumulative Percentage drug release of formulations with Xanthan gum (F_4-F_6)

Time(hr)	Cumulative % drug release F_4	Cumulative % drug release F_5	Cumulative % drug release F_6
0	0	0	0
1	3.99	3.74	3.35
2	10.31	9.45	8.12
4	19.15	17.34	16.69
6	28.76	27.68	25.42
8	39.35	36.93	34.25
10	51.59	47.41	43.85
12	63.79	58.79	54.56
14	75.59	70.63	65.42
16	84.65	80.72	75.14
18	92.41	87.52	82.24
20	97.19	92.74	87.28
22	99.98	96.27	90.71
24	-	98.15	92.64

Figure No 18: Cumulative percentage drug release of formulations containing Xanthan gum (F_4-F_6)

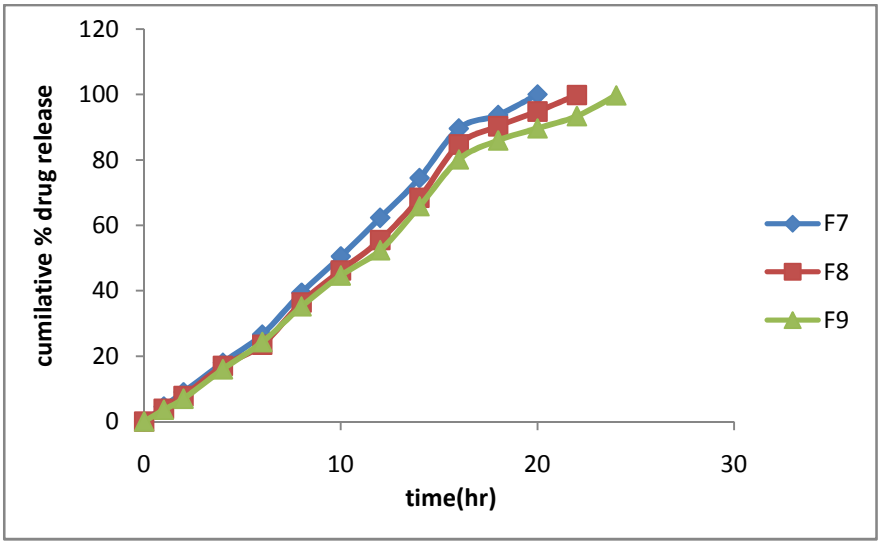


From the above figure no 21 it can be observed that the polymer xanthan gum has controlled effect on the release of drug from the controlled release matrix tablet. The percentage of drug release from formulations F_4, F_5 and F_6 was 99.98%, 98.15% and 92.64% in 24hr respectively. The difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer. The cumulative percent of drug release from various formulations and release coefficients values of the various models for respective formulation were represented in table no 16.

Table No 17: Cumulative Percentage drug release of formulations with combination of polymers (F_7-F_9)

Time(hr)	Cumulative % drug release F_7	Cumulative % drug release F_8	Cumulative % drug release F_9
0	0	0	0
1	4.54	3.84	3.61
2	8.99	7.78	6.99
4	18.29	17.12	16.89
6	26.61	23.45	24.31
8	39.37	36.39	35.21
10	50.45	46.19	44.68
12	62.29	55.47	52.42
14	74.42	68.36	65.85
16	89.58	84.69	80.14
18	93.69	90.27	85.97
20	99.98	94.78	89.67
22	-	99.79	93.41
24	-	-	99.74

Figure No 19: Cumulative percentage drug release of formulations containing Combination of polymers (F_6-F_9)



From the above figure no 22 it can be observed that the polymer HPMC K100 M and Xanthan gum has controlled effect on the release of drug from the controlled release matrix tablet. The percentage of drug release from formulations F_7, F_8, and F_9 were 99.98%, 99.79%, and 99.74% in 24hr respectively. These are the formulations done by combination of polymers. The cumulative percent of drug release from various formulations and release coefficients values of the various models for respective formulation were represented in table no 17.

The percentage of drug release from formulations F_2, F_3, F_5, F_6 and F_9 was found to be 97.27%, 90.81%, 98.15%, 92.64% and 99.74% in 24 h respectively. The formulationsF_1, F_4, F_7 and F_8 was found to be 90.45%, 92.41%, 93.61% and 90.27% respectively.

The formulations F_1, F_4, F_7 and F_8 were failed to release drug up to 24 hr and formulation with combination of polymers (HPMC K100 M & XANTHAN GUM) in 1:1 ratio was released drug 99.74% in 24 hrs.

Formulation F_9 was considered as best formulation among all formulations and controlled the drug release for desired period of time (24hrs). Hence F_9 chosen for kinetic studies.

7.7 RELEASE KINETICS

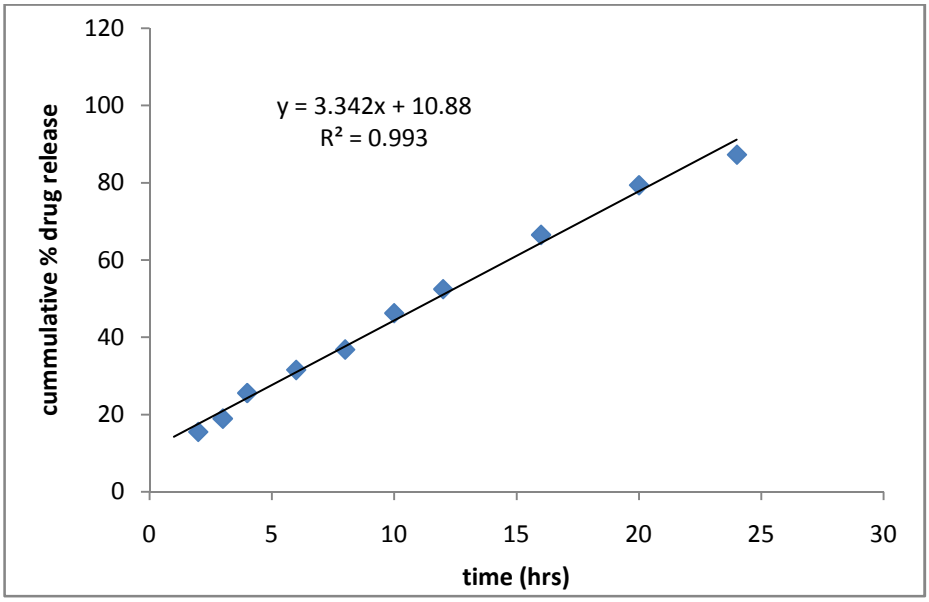
Table No 18: Release kinetics of the optimum formulation

Time (hr)	√T	Log T	Cumulative % drug dissolved	Cumulative % drug un dissolved	Log Cumulative % drug dissolved	Log Cumulative % drug Un dissolved
0	0	0	0	100	0	2
1	1	0	3.61	96.39	0.557	1.98
2	1.414	0.301	6.99	93.01	0.844	1.96
4	2.0	0.60	19.57	80.43	1.29	1.90
6	2.44	0.778	25.31	74.69	1.40	1.87
8	2.8	0.90	35.21	64.79	1.54	1.81
10	3.16	1.0	44.68	55.32	1.65	1.75
12	3.46	1.079	52.42	47.58	1.719	1.67
14	3.74	1.146	65.85	34.15	1.818	1.53
16	4.0	1.20	80.14	19.86	1.90	1.29
18	4.2	1.255	85.97	14.03	1.93	1.14
20	4.47	1.30	89.67	10.33	1.95	1.014
22	4.69	1.34	93.41	6.59	1.97	0.818
24	4.89	1.38	99.74	0.26	1.998	-0.585

To know the mechanism of drug release from these formulations, the data were treated according to zero order (cumulative amount of drug released Vs time), first-order (log cumulative percentage of drug remaining Vs time), Higuchi's (cumulative percentage of drug released Vs square root of time), and Korsmeyer (log cumulative percentage of drug released Vs log time) equations.

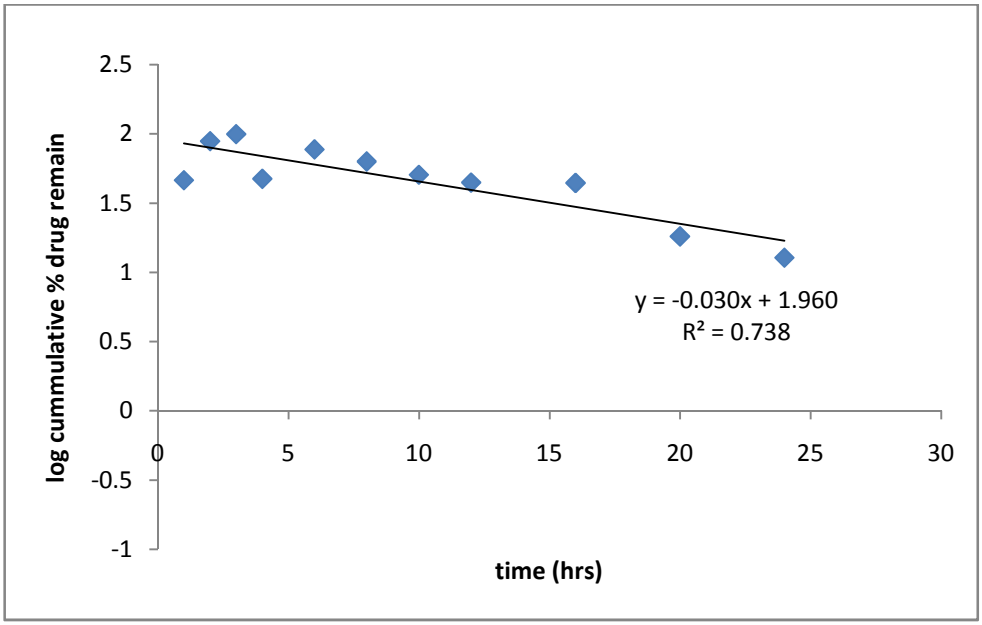
ZERO ORDER

Figure No 20: Zero order plot of F_9 Formulation



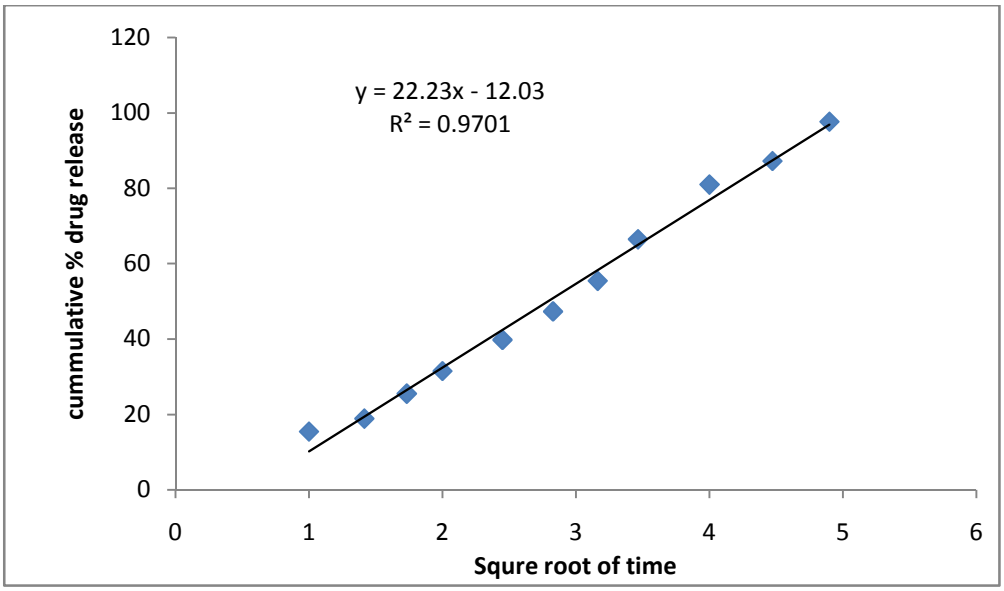
FIRST ORDER

Figure No 21: First order plot of F_9 Formulation



HIGUCHI MODEL

Figure No 22: Higuchi Plot for F_9 Formulation



KORSEMEYER PEPPAS MODEL

Figure No 23: Korsemeyer Peppas Model ForF_9 Formulation

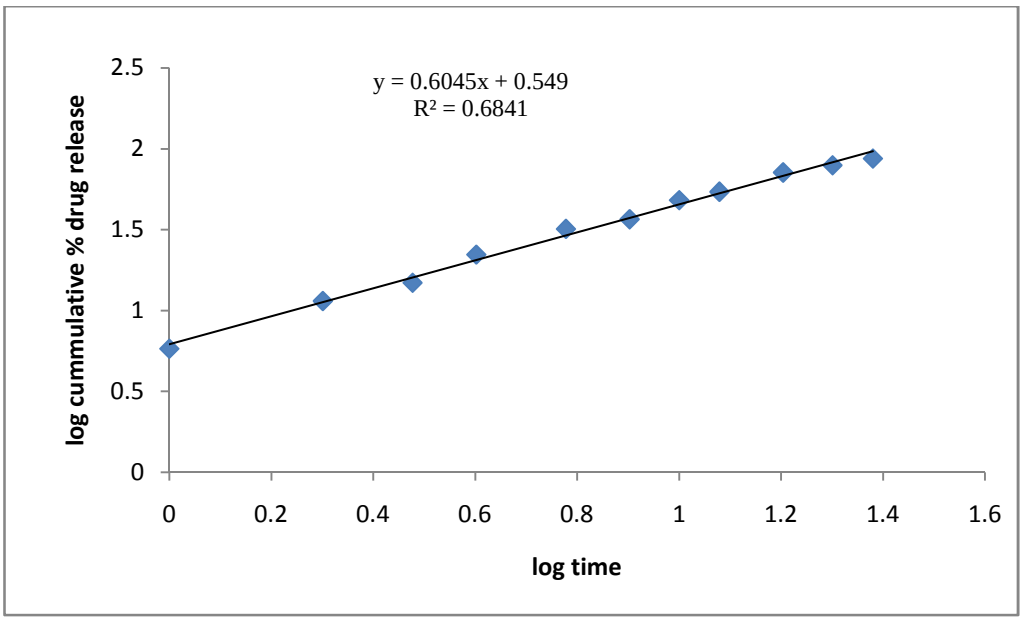


Table No 19: Release Kinetics of Perindopril Erbumine

Formulation	Zero – Order R^2	First-Order R^2	Higuchi R^2	Korsemeyer and peppas	
				R^2	N
F_9	0.993	0.738	0.9701	0.6841	0.6045

The *in vitro* release rate were fitted to Korsemeyer-peppas model and interpretation of release exponent value (n) enlighten in understanding the release mechanism from the dosage form. The release exponent value (n) obtained thus obtained was 0.6045.. The drug release was diffusion controlled as plot of Higuchi's model was found to be linear. The F_9 formulation exhibited anomalous (non Fickian) diffusion mechanism.

These Formulations are also showed as highest R^2 values of zero order kinetics indicating the amount of drug from the matrix system were by both diffusion and erosion.

Selection of optimized batch

The F_9 of controlled release matrix tablet was chosen as optimized formulation because it showed more linearity between the cumulative percentage perindopril erbumine versus time as indicated by the highest value of the correlation co-efficient in all selected models, among controlled release matrix tablet and best fitted for both Korsemeyer-peppas (0.6841) and zero order (0.993) model.

7.8 ACCELERATED STABILITY STUDIES

In any rationale design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection.

In the present study, stability studies were carried out on formulation $F_{9.}$ The tablets were stored at 40 ± 2^0 C and 75 ± 5 % RH for a duration of 3 months and analysed for their physical parameters, hardness, drug content and friability after 3rd month the data were showed in table no 20 and % drug release was shown in table no 21 and figure no 24.

Table No 20:

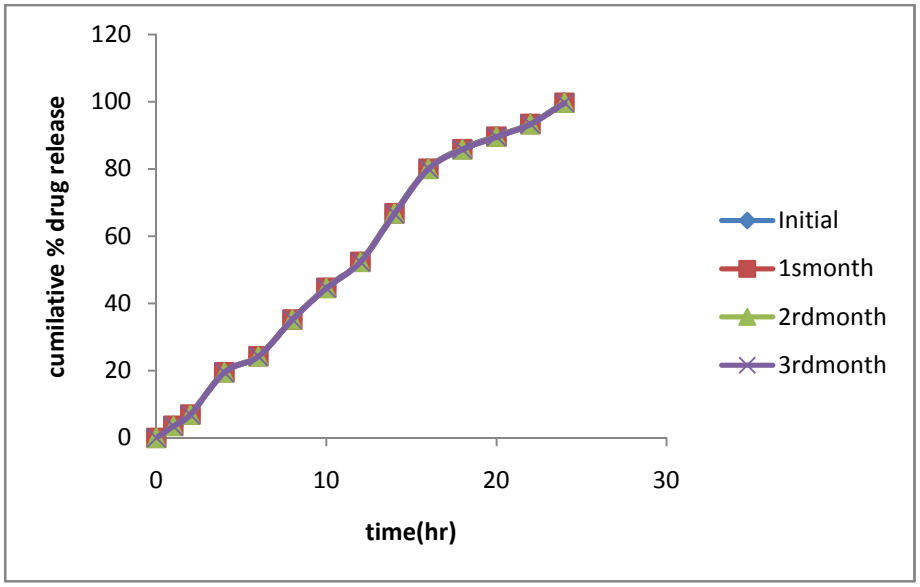
Characteristic of optimized perindopril erbumine controlled release matrix tablet

	Drug content (%)	**Hardness (kg/cm^2)**	**Friability (%)**
After one month	99.70±0.17	4.0±0.115	0.57
After 2nd months	99.66±0.15	4.0±0.10	0.60
After 3rd months	99.62±0.15	4.0±0.10	0.63

Table No 21: *In Vitro* Dissolution Studies

Time in hours	**Cumulative % drug release**			
	Initial	**1st month**	**2nd month**	**3rd month**
0	0	0	0	0
1	3.61	3.58	3.50	3.46
2	6.99	6.91	6.91	6.87
4	19.57	19.52	19.49	19.45
6	24.31	24.29	24.26	24.20
8	35.21	35.18	35.20	35.18
10	44.68	44.63	44.59	44.54
12	52.42	52.40	52.35	52.30
14	66.85	66.81	66.76	66.65
16	80.14	80.09	80.02	80.00
18	85.97	85.90	85.83	85.78
20	89.67	89.61	89.57	89.52
22	93.41	93.39	93.35	93.31
24	99.74	99.70	99.66	99.62

Figure No 24: Stability plot of F_9 formulation



Accelerated stability studies were carried out at 40^0 C and 75% RH for three months. After storage the formulation subjected to drug content, hardness, friability and *in vitro* dissolution studies showed no significant change.

There is no much change in accelerated stability studies hence the formulation F_9 was stable.

8. SUMMARY AND CONCLUSION

- The preformulation parameters like organoleptic properties, angle of repose, bulk density, tapped density, Hausner's ratio, carr's index and compressibility index of pure drug was evaluated and complied with the pharmacopoeia specifications.

- FTIR studies showed that there was no interaction between drug and polymer.

- Controlled release matrix tablets of perindopril erbumine was formulated by using polymer like HPMC K100 M and Xanthan gum.

- The formulated batches were evaluated for physicochemical parameters and dissolution profiles. The physical properties like hardness, weight variation and friability of majority of the batches complied with the pharmacopoeial specifications. The drug content of all tablets was in the range of 93 – 100%.

- *In vitro* dissolution study of all the formulations was done in acid buffer pH 1.2 and phosphate buffer pH 6.8. The release rate was faster with Xanthan gum compared to HPMC.It has been observed that using of combination of polymers (F_9) retarded the drug release up to 24 hrs satisfactorily. The cumulative % drug release was observed for F_9 formulation 99.74. Hence F_9 was taken for kinetic studies.

- The kinetic study was carried out for F9 which showed that the drug release follows zero order (regression coefficient 0.993) was adequately controlled the drug and anomalous non –fickian (N >5) transport of diffusion from the release from the formulation with complete release in 24hrs made it to select as an optimized formulation compared with other formulations.

- The accelerated stability studies were carried out for F9 formulation for 3 months. Data revealed that there was no considerable difference.

- From the above study, concluded that F_9 was the optimised formulation which has shown better drug release in 24hr. However further *in vivo* studies can be carried out to support the results.

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